Indoor air pollution and environmental tobacco smoke exposure in a South African birth cohort study.

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I, Aneesa Vanker, hereby declare that this thesis is my own work, both in concept and execution, apart from the normal guidance received from my supervisors and contributions by those acknowledged.

Published manuscripts form part of this thesis. Any assistance received with study management, data collection, analysis and review from co-authors of the manuscripts is described below:

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Contribution of student and co-authors:

I conceptualised the review under the supervision of RPG and HJZ and conducted the literature search and initial manuscript draft. Both RPG and HJZ reviewed the manuscript and added conceptual and intellectual comment. All authors were involved in the final draft of the manuscript.

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Contribution of student and co-authors:

I developed the study methodology together with my supervisors RPG and HJZ. Technical advice and expertise was provided by PDS. Together with WB we developed home visit protocols and sourced and implemented the equipment required to measure indoor air pollution (IAP). Fieldworker training and oversight was provided by me, with the assistance of WB. Field workers collected IAP measures and other data that was then supervised by WB and myself. SGS® environmental services performed IAP measure

analysis. Data analysis plan was conceptualised by myself with the statistical support of PMN. I completed the initial draft of the manuscript. All authors provided intellectual review and read the final manuscript prior to submission.

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I together with WB and HJZ conceptulised the study. DJS developed the psychosocial methodology. KB was responsible for data analysis. RPG, DJS, NK contributed to the study design. AV, WB, NK recruited patients and collected data. AV, BM, RPG and HJZ interpreted data. AV, KB, BM, HJZ drafted the manuscript All authors contributed to the writing of the manuscript and approved the submitted manuscript.

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I developed the study methodology with my supervisors RPG and HJZ, together with expert input from PDS. I supervised data collection together with support from WB. Together with LW and PMN we devised a data analysis plan and LW and PMN executed data analysis. The co-authors, RPG, PDS and HZ reviewed the manuscript and added conceptual and intellectual comment. All authors read the manuscript prior to submission and commented/contributed within their area of expertise.

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a. A. Vanker, R.P. Gie & H.J. Zar (2017): The association between environmental tobacco smoke exposure and childhood respiratory disease: a review. Expert Review of Respiratory Medicine, 2017 Aug;11(8):661-673 DOI: 10.1080/17476348.2017.1338949

b. Vanker A, Barnett W, Nduru PM, Gie RP, Sly PD, Zar HJ. Home environment and indoor air pollution exposure in an African birth cohort study. Science of the Total Environment. 2015;536:362-7.

c. Vanker A, Barnett W, Brittain K, Gie RP, Koen N, Myers B, Stein DJ, Zar HJ. Antenatal and early life tobacco smoke exposure in an African birth cohort study. Int J Tuberc Lung Dis. 2016;20(6):729-37.

d. Vanker A., Nduru P.M., Barnett W., Dube F.S., Sly P.D., Gie R.P., Nicol M.P., Zar H.J. Indoor Air Pollution and Tobacco Smoke Exposure: Impact on Nasopharyngeal Bacterial Carriage in Mothers and Infants in an African Birth Cohort Study. Submitted for editorial consideration: European Respiratory Journal Open Research April 2018 Minor revisions due 1 August 2018.

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Abstract

Childhood respiratory disease is the leading cause of under-5 mortality in low and middle-income countries (LMIC) and a major reason for health care visits and hospitalisation. Environmental exposures to indoor air pollution (IAP) or tobacco smoke are important risk factors for childhood respiratory disease. Despite increased electrification, many communities in LMIC rely on alternate fuel sources for household cooking or heating. The impact of antenatal or postnatal exposures on early childhood respiratory disease has not been comprehensively studied in LMIC especially in Africa.

The aim of this work was to investigate the impact of IAP and environmental tobacco smoke (ETS) exposure on child health and early-life respiratory disease in the Drakenstein Child Health Study (DCHS), a South African birth cohort study. The DCHS investigates the epidemiology and impact of early-life exposures on child health including lung disease. The study is set in a peri-urban poor community in the Western Cape, South Africa. Pregnant women were enrolled from two public primary healthcare clinics, Mbekweni (serving a predominantly black African population) and Newman (predominantly mixed-ancestry population) and 1000 mother-infant pairs longitudinally followed from birth through 1 year of life. The thesis chapters are presented as published manuscripts that describe IAP and ETS exposure in the 2 communities in the DCHS cohort from the antenatal period and the impact of these exposure on child health and lung diseases, LRTI and wheezing illness in the first year of life.

To measure exposures comprehensively, two home visits, one in the antenatal period (third trimester) and the second postnatally (between 4 and 6 months of the infant's life), were conducted to assess the home environment and to measure the most common indoor air pollutants and by-products of combustion. Devices placed in participants' homes measured exposure to particulate matter (PM_{10}), carbon monoxide (CO), nitrogen dioxide (NO_2), sulphur dioxide (SO_2) and volatile organic compounds (VOC). Maternal and infant urine cotinine measures were used to validate self-reported tobacco smoking and exposure. Study staff trained in recognition of LRTI or wheeze documented all episodes, which were categorised according to WHO case definition criteria.

Exposure to IAP was comprehensively assessed in over 800 homes antenatally and postnatally providing important South African data on IAP and potential sources of exposure. Tobacco smoke exposure was assessed longitdunially by maternal self-report using validated scales and by measurement of urine cotinine in mothers and infants. Tobacco smoke exposure was found to be highly prevalent with a smoking prevalence of >50% in mixed-ancestry mothers. Alarmingly, 18% of infants were born with urine cotinine levels in keeping with active smoking, while a further 30% had levels indicating passive smoke exposure.

Key findings were despite 92% of homes reporting access to electricity, there was still a reliance on cheaper alternate fuels. Tobacco smoking prevalence amongst pregnant women was high (32%), as was household exposure to tobacco smoke (44%). ETS exposure was associated with low birth weight and antenatal IAP or ETS exposure was significantly associated with increased LRTI. ETS exposure was also associated with wheezing illnesses. A novel finding was that antenatal exposure to toluene, a volatile organic compound, was associated with severe LRTI and hospitalisation.

The timing of environmental exposures on the subsequent development of LRTI in infancy has not been well described. An important finding was that antenatal exposures were the main risk factors associated with LRTI, with maternal smoking in pregnancy or PM_{10} exposure most strongly associated with LRTI. Wheezing illness was associated with both antenatal and postnatal maternal smoking and antenatal maternal smoke exposure and postnatal household member smoking. Both IAP and ETS exposure impacted on both maternal and infant nasopharyngeal bacterial carriage which may be a precursor to the development of LRTI.

Environmental exposures therefore had a substantial impact on child health and on LRTI and wheezing illness. The effect on LRTI of antenatal compared with postnatal exposure suggests an *in utero* developmental lung effect. This study highlights antenatal and early life as a critical period for lung development. Urgent and effective smoking cessation programmes targeting women of child bearing age as well as public health interventions to reduce IAP are required. Woman of childbearing age, pregnant women and children in poor communities represent vulnerable populations at risk for long-term health effects of these exposures.

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Abbreviations

ASSIST	Alcohol, smoking and substance involvement screening test
CI	Confidence interval
CO	Carbon monoxide
ETS	Environmental tobacco smoke
HIC	High income countries
HIV	Human immunodeficiency virus
IAP	Indoor air pollution
IQR	Interquartile range
IR	Incidence rate
LMIC	Low and middle-income countries
LRTI	Lower respiratory tract infections
NO_2	Nitrogen dioxide
OR	Odds ratio
PM_{10}	Particulate matter size 10um
PMTC	Prevention of mother to child transmission
RR	Risk ratio
SES	Socio-economic status
SGA	Small for gestational age
SO_2	Sulphur dioxide
VOC	olatile organic compounds
WfA Z-score	Weight for age z score

Indoor air pollution and environmental tobacco smoke exposure in a South African birth cohort study.

1 Introduction

Childhood respiratory disease is the leading cause of under-5 mortality in low and middle income countries (LMIC) and a major reason for health care visits and hospitalisation.[1, 2] There are many risk factors for developing respiratory disease, which may interact with each other to affect disease incidence and severity. Respiratory disease is a broad term and studies focus on one aspect such as pneumonia or wheezing disease, when in fact it is often difficult to separate different forms of LRTI. Therefore, the effects on lower respiratory tract infections (LRTI) in general should rather be considered. The Drakenstein Child Health Study (DCHS), a South African birth cohort study, was developed to investigate the early-life risk factors for child health including lung disease. The DCHS is set in a peri-urban, poor South African community in two suburbs, with a high prevalence of LRTI and many potentially deleterious exposures, which is typical of many LMIC settings and populations. A key focus has been on longitudinal assessment of the aetiology, prevalence and sequelae of early-life LRTI on child health.[3] Despite a global effort to improve electrification to under-resourced areas, the use of alternate fuel sources for household activities continues in many LMIC. Indoor air pollution (IAP) generated from this and the effects on child health in an African setting have not been well described.

Figure 1: Map of South Africa highlighting Cape Winelands area including Drakenstein district

Further, tobacco smoking remains a global problem with an increasing prevalence of smokers particularly in LMIC.[4] Atlhough the DCHS population is poor, electrification has occurred and there is increasing use of electricity as well as alternate fuels. This work explores the effects of these environmental exposures on child health and early-life respiratory disease within the DCHS.

2 Background and Literature Review

2.1 Childhood Respiratory Diseases

Respiratory diseases have long been recognised as the leading cause of childhood death or illness with infants and young children most vulnerable. Global efforts to address this through widespread implementation of new vaccines; including pneumococcal conjugated vaccine, better nutrition, improved case-management algorhithms and better prevention and treatment of HIV as well as setting millennium development goal 4 (MDG 4) as a two-thirds reduction in LRTI mortality by 2015, has resulted in much progress in the management of childhood LRTI as well as a substantial reduction in the number of LRTI deaths in the last two decades.[5-7] However, despite these advances, LRTI including pneumonia and wheezing illnesses remain the leading cause of under-5 morbidity and mortality with almost 1 million deaths a year.[5, 8-10]

Infancy and early childhood are the most vulnerable period for the development of LRTI. Strategies to control both the morbidity and mortality in infancy and childhood associated with LRTI include providing a healthy environment, preventing the development of respiratory illnesses and appropriately treating children who become ill.[6] Many of these strategies address well established risk factors for LRTI including the protective role of breastfeeding and appropriate nutrition in early life, immunisation against vaccine preventable illnesses, prevention and then appropriate management of conditions including HIV and adequate treatment of co-morbid conditions.[8, 11, 12] Through these sustained efforts, a notable reduction in LRTI mortality has occurred, however these interventions have not been enough to large portions of LMIC reaching MDG 4.

Environmental factors are increasingly recognised as risk factors for childhood respirato-

ry diseases and for severe disease.[2, 13, 14] The role of exposure to indoor air pollution (IAP) or exposure to tobacco smoke on the development of childhood respiratory disease in African children has not been well studied. Identification of environmental determinants is important to effect appropriate interventions and strengthen public health strategies to prevent such disease. Further, the timing of these environmental exposures on the development of respiratory diseases has not been well delineated. It is well-recognised that antenatal exposure to tobacco smoke impacts foetal lung growth, [5, 16] yet the long-term consequences and cumulative effect of antental and postnatal exposure on the development of lung disease in infancy are less clear.

2.2 Indoor Air Pollution (IAP)

2.2.1 Defining household indoor air pollution (IAP)

Household indoor air pollution is generated by the use of alternate fuel sources for cooking and heating. Fuel sources can be categorised as solid fuels such as coal, biomass fuels including wood (unprocessed and charcoal), dung and crop residues and non–solid fuels like paraffin, liquefied petroleum gas, gas and electricity.[17] As fuels become cleaner and more efficient, they also becomes more costly. The “energy ladder” is a model used to describe household fuel choices in which differences in the use of energy is ascribed to socioeconomic status.[18] Fuels that require combustion result in numerous by-products which contribute to household indoor air pollution. There are over 200 by-products of combustion, the majority of which are of inhalable size. The more common measured inhalable chemicals and compounds include, particulate matter (10um and smaller), nitrogen dioxide, sulphur dioxide, carbon monoxide and the volatile organic compounds.[19-21]

IAP may also be influenced by the levels of outdoor air pollution. Road traffic, pollution from industry and agricultural practices may lead to increased household levels of IAP. [22] Other factors influencing IAP include environmental and household characteristics which impact on exposure levels. Single roomed homes, unventilated cooking and heating and overcrowding all contribute to higher levels of exposure.[23-27]

2.2.2 IAP – a global problem

Ambient air pollution is recognised as a major contributor to disease with household air pol-

lution ranked tenth as a risk factor for increased mortality. [28] In 2015, diseases caused by pollution were responsible for 16% of premature deaths worldwide, triple that from tuberculosis, AIDS and malaria combined.[22] Children are particularly susceptible to the effects of pollution, even at low doses, and are vulnerable during in-utero and early-life periods with potential lifelong effects.[22] Globally it is estimated that a third of the world's population rely on alternate fuel sources for domestic energy. [20, 29] Access to electricity is not universal especially in LMIC. Alternate fuels are often derived from local available sources that are dependent on geographical location. In Africa and India wood and charcoal are more commonly used compared to China where coal is more available.[29] In areas with limited fuel sources, there is often a reliance on household rubbish and plant residues for fuel, however, in peri-urban areas fuel sources may include paraffin or charcoal.

The use of alternate fuels is clearly linked to poverty. Worldwide, areas that rely on alternate fuels are also those with resource constraints, particularly in Africa and south-east Asia.[17, 29]

2.2.3 IAP – the South African context

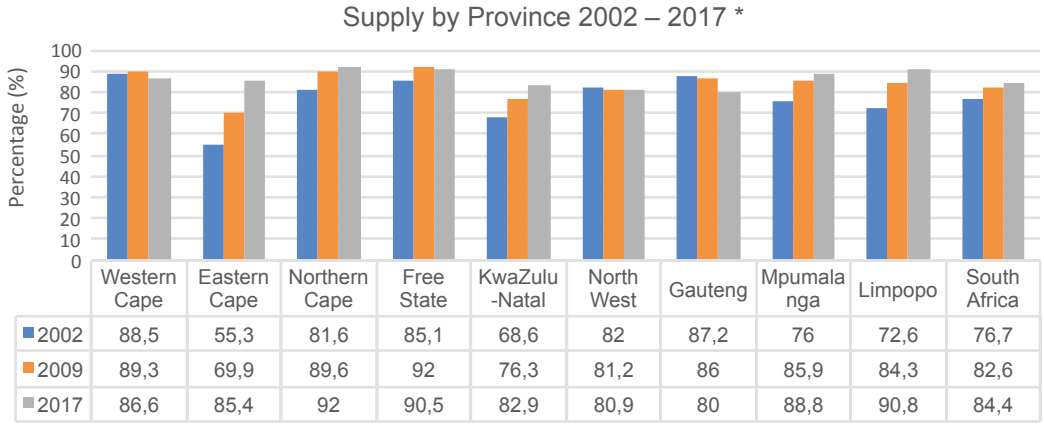
In South Africa there has been a drive to increase electrification especially to rural areas. This has resulted in a national increase in households connected to the main electricity supply to 85% in 2012. However, despite this, on average 62% of homes reported interruptions to power supply in the preceding 6 months.[30] Furthermore, nationally a quarter of homes in spite of electricity being available still relied on alternate fuels for cooking and this was as high as 50% in certain areas.[30, 31]

Other environmental determinants that contribute to IAP include household factors such as dwelling type, access to basic amenities and socioeconomic status. Assessing poverty relies on multiple factors. The multidimensional poverty index (MPI), an international measure of poverty, can be used compare poverty between areas, using 3 broad dimensions; health, education and living standard.[31, 32] In South Africa, using this system, 8% of households were deemed to be poor. However, the intensity of deprivation based on weighted indicators was on average more than 40%.[31]

While there is limited South African data on the effects of IAP on child lung health, a large study using reported alternate fuel use data from 1998 found nearly half of households surveyed used polluting fuels and was significantly associated with under 5 year-old mortality[33] and another study found that almost 20% of homes used solid fuels with an increase in mortality and resultant loss of healthy life years.[34] These studies represent fuel use prior to the implementation of widespread electrification. However, more recently the use of "non-electrical" fuels for cooking and heating was associated with with a significantly higher prevalence of respiratory symptoms in school children surveyed in two South African towns.[35] Also children living within the Durban metropole, South Africa were found to have relatively high levels of PM_{10} within homes. Predictive models suggested that type of housing structure, household smokers or primary fuel used were the largest contributors to this.[36]

2.2.4 Measuring IAP

Figure 2: South African Households Connected to Electricity



	Western Cape	Eastern Cape	Northern Cape	Free State	KwaZulu -Natal	North West	Gauteng	Mpumalanga	Limpopo	South Africa
2002	88,5	55,3	81,6	85,1	68,6	82	87,2	76	72,6	76,7
2009	89,3	69,9	89,6	92	76,3	81,2	86	85,9	84,3	82,6
2017	86,6	85,4	92	90,5	82,9	80,9	80	88,8	90,8	84,4

* Adapted from Statistics SA General Household Survey 2017 [30]

Measuring household IAP is a challenge with most studies relying on reported exposure or extrapolating levels from sampling of a few homes.[29, 37, 38] The lack of standardisation in assessing IAP makes it difficult to compare outcomes between studies.[39-42] Studies that assess IAP broadly employ one the following methods; modelling studies, health outcome studies, exposure measurement, a combination of exposure and health out-

come or intervention studies with improved combustion devices.[40] However, the complexity in assessing exposure in terms of direct measurement and other environmental factors with the potential to introduce bias is evident. [41]

The numerous challenges involved in quantifying IAP include factors related to the home, the equipment used to measure pollution, the nature of the pollutants and duration of exposure.[39, 40] Outdoor air pollution may also influence IAP levels and this may be difficult to fully account for.[43] The position and size of the home, type of kitchen and ventilation all play a role in household IAP.[23, 29]

There are several barriers to measurement of IAP in resource-limited settings, Equipment needs to cost-effective, robust and acceptable to the community in which it will be used.[29, 44] Many of the commercially available equipment are dependent on a battery or power-source to work. This is a limiting factor in terms of duration of monitoring.[44] This also leads to an average exposure calculated which may underestimate effects associated with peak exposure.[29] Positioning of measuring devices in the home is important as this can lead to either over or under assessment of household pollution levels, depending on where the equipment is placed; such placement may be especially challenging in very small poor homes. [17, 23, 29]

Direct measures of household IAP include devices that measure for common pollutants. Carbon monoxide, nitrogen and sulphur dioxide, particles and volatile organic compounds are the principle combustion pollutants.[42] Particulate matter and carbon monoxide are most commonly measured as they are considered the most health damaging and are produced with all forms of combustion.[44] Particulate matter of size 2.5um ($PM_{2.5}$) or 10um (PM_{10}) are the sizes most commonly measured as these are of inhalable size. Other by-products of solid fuel burning include nitrogen dioxide and sulphur dioxide. Non-solid fuel sources such as paraffin are more likely to produce volatile organic compounds including benzene, toluene and xylene.[20, 45]

The complex relationship between pollutant levels and human exposure make it difficult to define clear guidelines on acceptable IAP levels. Various countries, including South Africa, have devised local ambient air quality standards, however, these are often vari-

able, and increasingly lower standards have been recommended with recognition of the health effects associated with air pollution exposure.[19, 45, 46]

Owing to the difficulties of directly measuring IAP in households, a number of studies have relied on reports of alternate fuel used and correlated this to respiratory disease in children.[47-51] These include case-control and large population based studies all showing significant associations between the use of alternate fuels and varying respiratory symptoms,[47, 48] while other studies depended on inferring exposure using outdoor air quality monitors and modeling this to exposure in participants homes.[52-55]

2.3 Tobacco smoking and environmental tobacco smoke exposure (ETS)

2.3.1 Defining ETS exposure

While the direct harms of tobacco smoking are well known, the consequences of tobacco smoke exposure from second-hand smoking has gained recognition as a cause for morbidity and premature mortality.[56] Second-hand smoke is generated from the burning end of a tobacco product, including cigarettes and the smoke exhaled by the smoker, which contains thousands of chemicals and many carcinogenic and toxic compounds.[57] Third-hand smoke, refers to the residual tobacco smoke contamination that remains after the cigarette is extinguished[58] and poses a further potential continued health risk.[59] In-utero tobacco smoke exposure is usually the first point of ETS exposure to the developing foetus. This may result directly from maternal smoking or from maternal smoke exposure.[56, 60] The level of foetal smoke exposure is dependent on a number of factors including the brand of cigarette smoked, the depth of inhalation and individual uptake and metabolism of the cigarette smoke components.[61]

2.3.2 ETS exposure – a global problem

With an estimated 1.3 billion smokers world-wide and more than 80% living in LMIC[56, 62] the risk of tobacco smoke exposure is high, particularly for vulnerable groups including infants and children. While smoking prevalence is decreasing in high income countries (HIC), the converse is true of the LMIC where smoking rates are increasing.[4, 62] Globally there are very high childhood ETS exposures reported ranging from over 60% in certain European regions to 12% in Africa with a worldwide average of 40% [4] Despite global ef-

forts to regulate the tobacco industry including banning advertising of tobacco products and smoking in public areas in some countries,[57, 62] these policies do not protect against household exposure to tobacco smoke. Children remain susceptible to this exposure from either mothers or other household contacts who smoke. Tobacco smoke exposure in infants also may begin antenatally in pregnant women who smoke and continue through childhood. Underreporting of smoking and exposure, particularly in pregnant women is common. The pooled prevalence for tobacco use in pregnant women from LMIC was reported as 2.6% (95% CI 1.8-3.6), with current tobacco smoking in pregnant African women being 0.6% (95% CI 0.3-0.8) in the African region, however, this was based on self-reported data and tobacco smoke exposure was not assessed.[63]

2.3.3 ETS exposure – the South African context

South African prevalence data also confirmed that a large proportion (17.6% (95% CI 6.3 - 18.9) of South African adults continue to use tobacco, with the highest current tobacco prevalence being in the Western Cape province (32.9%). Further, overall males had a four times high prevalence than females; 29.2% vs 7.3%.[64] Smoking prevalence in South Africa has decreased from 24.6% in 1998 and may be attributable to tobacco control legislation.[65] South African government implemented tobacco control measures have led to a reduction in cigarette use amongst school learners over a 12-year survey period. However, of concern was the smaller reduction in smoking prevalence seen amongst girls.[66] Although The Global Youth Tobacco Survey has also reported a decrease in tobacco smoke exposure in South African school-going adolescents, 25.7% of students were still exposed to tobacco smoke within their homes and 34.2% outside their homes.[67]

South Africa has adopted a number of tobacco control measures and is part of the World Health Organization's (WHO) Framework Convention on Tobacco Control (FCTC).[68-70] Despite this, another large study of over 3000 South African adults assessed tobacco smoke exposure amongst non-smoking adults and found 55.9% reported smoke exposure in the home, workplace or at a hospitality venue. This highlights the need for comprehensive smoke-free laws that prohibit smoking in all public indoor areas without exemptions.[71]

2.3.4 Measuring ETS exposure

Maesuring exposure to ETS is difficult with prevalence data relying on self-reports of smoking and exposure. This is often under-reported with the true magnitude of exposure remaining relatively unknown.[4, 56, 67, 72] Biomarkers of tobacco smoke are useful in quantifying both smoking prevalence and exposure, however, the invasive nature of many of these tests makes the widespread use in epidemiological studies difficult.[73, 74] While there are a number of emerging biomarkers of tobacco smoke, cotinine, a metabolite of nicotine, remains a reliable measure of both tobacco smoking and exposure.[75] Cotinine can be tested for in blood, urine, saliva or hair and has been found to be a very stable metabolite of nicotine with good correlation to nicotine levels. The ability to quantify cotinine levels also makes it a useful marker to differentiate between tobacco smoking and exposure.[74, 76]

2.4 Environmental exposures and childhood respiratory disease

Lung development commences in utero from the embryonic phase with maturation continuing into adolescence, thus making it highly susceptible to environmental exposures in this time. [77] Increasing evidence suggests that alveolarisation continues into adolescence and beyond, with the potential for recovery from early-life insults, however conversely environmental and other exposures may further affect lung growth in this time. [78, 79] ETS exposure and ambient air pollutants were found to impair both lung growth and architecture, leading to respiratory impairment after birth.[77] A complex interplay of factors may contribute to the effect of environmental toxins on the foetus, including the direct effect of nanoparticles inhaled by the mother crossing the placenta, as well as the induction of a systemic immune or inflammatory response in the mother causing oxidative stress and placental insufficiency. Nicotine is the major component of tobacco smoke found to affect lung growth and alveolarisation by interaction with nicotinic acetylcholine receptors (nAChR) leading to cell proliferation and dysanaptic lung growth and by reducing the surface complexity of the lung parenchyma, increasing collagen accumulation, upregulating surfactant protein gene expression, and inducing neuro-endocrine cell hyperplasia in fetal lungs, all leading to altered pulmonary function.[80, 81] Further, these insults may cause epigenetic changes all of which impact on post-natal lung health.[82, 83] Prenatal air pollution exposure was also found to alter immune competence with the

alteration of cord blood natural killer (NK) cells and T-lymphocytes which may play a role in long-term allergic conditions.[84]

Children's susceptibility to air pollution is increased due to a number of factors including, vulnerability of the developing airways, an immature immune system, increased ventilation and greater proportion of time spent indoors compared to adults.[85] Air pollution including tobacco smoke affects respiratory defence mechanisms at a number of levels with each level of the respiratory tract attempting to filter out the constituents of air pollution.[21] Ultrafine particles however, can rapidly pass into the systemic circulation and may induce a systemic response.[86] IAP and ETS may also lead to epithelial inflammation allowing for organisms to breach the epithelial barrier more easily.[87-89] Mice models have also shown an increase in proinflammatory cytokines with resultant computed tomography (CT) scan changes in particulate matter exposed mice.[90] Another animal study also found that nicotine induced epithelial-mesenchymal transition (EMT), a process activated following lung injury, contributes to lung fibrosis.[91]

2.4.1 IAP and lower respiratory tract infections (LRTI)

In children under 5 years of age, household air pollution is the 7th leading risk factor for death due to its impact on acute lower respiratory infection.[28] A large number of studies from both HIC and LMIC explored the associations between IAP and a number of childhood respiratory outcomes [52, 92] with 2 published meta-analyses. Dherani *et al* calculated a summary odds ratio of IAP and LRTI of 1.78 (95% confidence interval, CI: 1.45–2.18),[38] while Po and colleagues found an almost just over 2 times higher OR 3.53 (95% CI 1.94 to 6.43).[93] The differences found may be attributed to the definition of IAP used in each study and the outcomes (LRTI versus respiratory disease in general.) Similarly, another systematic review aimed at establishing a quantitative association between IAP, acute LRTI and low birth weight (LBW) in under-5 children, found that the risk of acute LRTI increased 2.51 times and that of LBW 1.45 times due to IAP exposure.[94]

Studies assessing IAP and respiratory disease in children are area specific and air pollutants depend on the predominant fuel source used. However, the major by-products of combustion are generally the same. The effects of IAP are also dependent on other

factors including the home environment and the intensity and duration of exposure. In a large Indian rural cohort, children from households that used solid fuels were almost twice as likely to develop LRTI than those from households that did not [OR1.78 (95% CI: 1.05-2.99)][95] In a seperate case-control study, also from India, the use of biomass fuels for cooking, was associated with an almost five-fold risk of developing acute LRTI (adjusted OR 4.73, 95% CI 1.67–13.45).[96] A case-control Nepalese study demonstrated an increased risk of acute lower respiratory infections associated with any use of biomass stoves [odds ratio (OR) = 1.93; 95% CI: 1.24, 2.98], kerosene stoves (OR = 1.87; 95% CI: 1.24, 2.83), and gas stoves (OR = 1.62; 95% CI: 1.05, 2.50) compared to electric stoves.[97] Data from Africa also found an increased prevalence in acute respiratory infections in Ethiopian children exposed to biomass combustion, OR2.97 (95% CI: 1.38-3.87) and kerosene, OR1.96 (95% CI: 0.78-4.89) fuels in their homes.[98] Similarly, in Zimbabwean children under 5-years of age, household use of biomass fuels more than doubled the risk of acute respiratory infections (OR 2.20; 95% CI: 1.16 - 4.19) compared to children from homes that used cleaner fuel sources (e.g. kerosene).[99]

Exposure to particulate matter, has also been associated with the development of LRTI in several studies. A systematic review and meta-analysis on the global burden of LRTI from particulate matter exposure, found most studies were from high income countries with low levels of particulate matter ($PM_{2.5}$) exposure and that data from Africa was underrepresented. The summary estimate of the meta-analysis, was a 1.12 (95% CI 1.03-1.30) increased risk in LRTI occurrence per 10 micrograms per meter cubed (10 ug/m^3). increase in annual average $PM_{2.5}$ concentration. [100] However, a birth cohort study from Bangladesh, measured $PM_{2.5}$ levels in the infants' sleeping rooms and found an increased risk of developing LRTI in infants who were exposed to increased levels of $PM_{2.5}$ (adjusted incidence rate ratio (IRR) 1.07, 95% CI 1.01-1.14).[101] Further, increased concentrations of $PM_{2.5}$ (exceeding 100ug/m3) were associated with a 12% decrease in age to the child's first acute LRTI.[102] $PM_{2.5}$(aOR 2.89, 95% CI 1.09-7.68), PM_{10} (aOR 5.50 95% CI 1.69-17.91) and CO (aOR 6.024, 95%CI 1.65-22.00) were also significantly associated with wheezing illness in Malaysian pre-school children[103] and in a pilot study from India, in homes that had higher measured levels of $PM_{2.5}$, increased respiratory illness was found in children. This was also noted in homes using biomass fuels and was

associated with the number of family members in the household.[104] Further, a study on the effect of particle size and concentration showed that smaller particles (mass concentration) (<1um) and the number concentration of particles (>5um) impacted on the development of respiratory symptoms and bronchitis.[105] Interestingly, even prenatal exposure to $PM_{2.5}$, independent of postnatal IAP exposure, increased the risk of recurrent pulmonary infections (aOR OR = 2.44, 95%CI: 1.12 – 5.36).[106] However, even exposure to larger size particulate matter (PM_{10}) was associated with increased frequency of LRTI in both children and adults.[107]

The impact of IAP on severe LRTI and LRTI -associated mortality is also significant. A global estimate of annual childhood disease burden from IAP exposure suggests 455 000 deaths and loss of 39 100 000 disability-adjusted life-years in under 5-year old children.[108] In a systematic review of IAP exposure on child survival, the pooled odds ratio for IAP exposure and childhood, including severe and fatal LRTI was 1.73 (95% CI=1.47, 2.03). However, when considering only fatal LRTI, the pooled OR was 2.80 (1.81, 4.34) p<0.000.[109] This was consistent with another systematic review looking at the risks for severe childhood LRTI which also found IAP exposure to be associated with this, OR1.57 (95% CI1.06-2.31).[110] Solid fuel use was also implicated in acute LRTI mortality in African children (adjusted hazards ratio 2.35 (95% CI 1.22 to 4.52) and the risk was increased in homes with poor ventilation (absent chimney or hood); adjusted hazard ratio 2.68 (95% CI 1.38-5.23).[51]

2.4.2 Environmental Tobacco Smoke (ETS) exposure and child health

The impact of tobacco smoke exposure on child health is increasingly recognized with children remaining vulnerable to the effects from the antenatal period through childhood.[111-113] Antenatal ETS exposure can affect somatic growth as well as have a developmental effect on lung growth.[15, 114] As lung growth trajectories are set in early life, such exposure may predispose to development of adult respiratory illness.[115] The timing of exposures may also influence outcomes. While the effects of antenatal tobacco smoke exposure on birth outcomes is well described,[111] the effect of antenatal versus postnatal exposures on respiratory illness in children is less clear with differing evidence on which time period has the most significant effects on asthma or wheezing illness.[116, 117]

In summary, there is an increased awareness that both indoor air pollution and environmental tobacco smoke exposure may impact on child health and LRTI which remain a leading cause of childhood morbidity and mortality. However, there is limited data from LMIC and in particular Africa.

3 Aim

The aim of this study was to investigate the impact of antenatal and early life exposure to indoor air pollution or environmental tobacco smoke on child health in the DCHS, a South African birth cohort study.

3.1 Hypothesis

IAP or ETS exposure is prevalent in pregnancy in this cohort , and is associated with impaired birth outcomes and LRTI or wheezing in infants and young children.

3.2 Specific aims included:

i. To describe the home environments and measure IAP in the DCHS, a birth cohort study in the Western Cape.

ii. To measure antenatal and early-life tobacco smoke exposure and investigate the association with birth outcomes in the DCHS.

iii. To longitudinally investigate the impact of antenatal and postnatal IAP or ETS exposure on nasopharyngeal bacterial carriage in mothers and infants in the DCHS, from birth to one year of age.

iv. To longitudinally investigate antenatal and postnatal exposure to IAP or ETS and the association with LRTI or wheezing illness in the first year of life in children in the DCHS.

4 Research Setting

Drakenstein Child Health Study (DCHS)

The Drakenstein Child Health Study (DCHS), a South African birth cohort study of 1000 mother-child pairs, longitudinally investigates the epidemiology, risk factors, aetiology, and long-term outcome of childhood diseases including respiratory illnesses.[118] The study site is in a peri-urban, poor socio-economic community in the Drakenstein sub-district, 50km from Cape Town. Pregnant women were enrolled from two public primary health care clinics, Mbekweni (serving a predominantly black African population) and Newman (predominantly mixed ancestry population) and all deliveries occurred at a single central hospital, Paarl hospital. Children are followed until at least 5 years of age.

5 Ethical Considerations

The study was approved by the Human Research Ethics Committees of the Faculties of Health Sciences, University of Cape Town and Stellenbosch University, and by the Western Cape Provincial Health Research committee (HREC 149/2013). Mothers provided written informed consent at enrolment; renewed annually.

6 Chapters

The subsequent chapters address the following:

Chapter 2: presents a literature review on the epidemiology of ETS exposure and the

effect on acute respiratory infections, chronic respiratory conditions and lung function in children.

Chapter 3: describes the home environment of the participants' and the methodology and process of measuring household indoor air pollution. It further expands on using urine cotinine as a quantitative measure of tobacco smoking and exposure.

Chapter 4: provides urine cotinine validated prevalence data on tobacco smoking and exposure in two disparate African communities. It also explores the association with birth outcomes in this birth cohort.

Chapter 5: focuses on antenatal and postnatal IAP and ETS exposure and nasopharyngeal bacteria carried in both mothers and infants.

Chapter 6: explores the effect antenatal versus postnatal IAP and/or ETS exposure on LRTI and wheezing in the first year of life as well the effects on severity of LRTI.

Chapter 7: Summary and recommendations.

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The association between environmental tobacco smoke exposure and childhood respiratory disease: A Review.

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Abstract

Introduction: Childhood respiratory illness is a major cause of morbidity and mortality particularly in low and middle-income countries. Environmental tobacco smoke (ETS) exposure is a recognised risk factor for both acute and chronic respiratory illness.

Areas covered: The aim of this paper was to review the epidemiology of ETS exposure and impact on respiratory health in children. We conducted a search of 3 electronic databases of publications on ETS and childhood respiratory illness from 1990-2015. Key findings were that up to 70% of children are exposed to ETS globally, but under-reporting may mask the true prevalence. Maternal smoking and ETS exposure influence infant lung development and are associated with childhood upper and lower respiratory tract infection, wheezing or asthma. Further, exposure to ETS is associated with more severe respiratory disease. ETS exposure reduces lung function early in life, establishing an increased lifelong risk of poor lung health.

Expert commentary: Urgent and effective strategies are needed to decrease ETS exposure in young children to improve child and long-term lung health in adults especially in low and middle income countries where ETS exposure is increasing.

1 Introduction

Childhood respiratory illness remains a major challenge for global health. Pneumonia is the leading cause of under-5 mortality outside the neonatal period in low and middle-income countries (LMICs).[1, 2] Asthma is the commonest chronic disease in children in high and LMIC settings.[3] Environmental tobacco smoke (ETS) exposure is a well-recognised risk factor for acute and chronic respiratory illness;[4] tobacco use is the leading global cause of preventable death.[5] Despite worldwide initiatives to reduce tobacco smoking, it is estimated that up-to 40% of children are still exposed to tobacco smoke[6] and approximately 6 million deaths are tobacco related with half a trillion dollars in tobacco related economic damage.[5] While the incidence of smoking is decreasing in certain regions,[7] it is increasing in others, particularly in LMICs and especially amongst women.[5, 8] Further, bans on tobacco smoking in public do not prevent smoking in homes where women and children may experience ETS exposure from household members,[8] with the magnitude of exposure closely related to cohabitants smoking habits.[9]

ETS exposure often begins in utero with maternal smoking or exposure. Antenatal or early-life ETS exposure, from maternal, household or community contacts, may impact on the susceptibility of the infant to develop respiratory disease and impair lung development.[10, 11] However, the effects of postnatal tobacco smoke exposure may also be substantial, leading to poorer respiratory health.[12]

Potential mechanisms for ETS induced damage include impaired in utero lung growth from suppression of foetal breathing or direct genotoxicity.[13] Tobacco smoke comprises a large number of chemicals and carcinogens, all of which may affect the developing respiratory system.[14] Animal models suggest that nicotine is the component that has significant detrimental effects on lung growth and collagen deposition.[15] Nicotine affects lung branching through stimulation of alpha- 7 nicotinic acetylcholine receptors during the pseudoglandular phase resulting in dysanaptic lung growth.[16] Changes in conducting airway structure can lead to decreased airflow and increased resistance, decreasing pulmonary function.[15, 16] Prenatal nicotine may also alter peripheral and central chemoreception.[14]

Further, there is evidence linking the effects of tobacco smoke exposure to impaired early-life immune function resulting in an imbalance in Th1 and Th2 responses increasing the susceptibility to allergic diseases and childhood respiratory infections.[14, 17]

The aim of this paper was to review the current data on the epidemiology of ETS exposure and the effects of this on lung health in children. Specific objectives were to investigate the effect of ETS exposure on acute respiratory infection, on chronic respiratory disease, and on lung function.

2 Methods

Searches were conducted of three electronic databases, PubMed, Scopus and Google Advanced Scholar. Keywords included, tobacco smoke or cigarette*, child*, respiratory or lung*, exposure or illnesses. Searches were limited to English language articles to include publications from 1990 – 2016. As this was not a formal meta-analysis, an adaption of the PRISMA guideline was used.[18]

All papers including meta-analyses and systematic reviews were reviewed and included. Abstracts of identified documents were read and full texts of relevant documents were retrieved. Reference lists of retrieved documents were also searched to identify additional publications. Records were screened to identify the original articles, reviews and meta-analyses relating to: epidemiology, ETS exposure and respiratory tract infection in children; chronic lung diseases (asthma and chronic obstructive pulmonary disease (COPD); and lung function. The majority of these (n=4422) were excluded as they were either included in systematic reviews or meta-analyses, or assessed as being not relevant to the above criteria. When multiple reports on the same area of knowledge were encountered the best quality article were selected for the review. From the 262 screened records, 123 were eligible for inclusion in the qualitative synthesis. (Fig 1).

3 Results and Discussion

3.1 Results

The 123 articles included were chosen to review the available literature on ETS exposure and childhood respiratory disease. In order to comprehensively review this extensive subject, literature pertaining to the epidemiology of ETS exposure, the acute and chronic sequelae and preventative strategies to limit exposure was then explored as described below.

3.2 Epidemiology of environmental tobacco smoke (ETS) exposure in childhood

Recent global estimates report that worldwide 40% to 70% of children are exposed to tobacco smoke. [6, 19] Further, the burden of antenatal exposure may be underestimated as smoking during pregnancy is often under-reported.[20, 21] There is large variability in smoking prevalence in different regions.[20, 22] The reported overall pooled prevalence of smoking during pregnancy in LMICs is 1.3% (95% CI 0.9 – 1.8%) with Southeast Asia having the highest pooled regional prevalence of 2.7% (95% CI 1.1-4.8).[20] However, this prevalence is based on self-reported smoking and may likely under estimate the true prevalence. (Table 1) Smoking in pregnancy may also depend on societal acceptance as demonstrated by very disparate smoking prevalence found in two closely located South African communities of different ethnicities; 51% in pregnant women from one community compared to 14% in the other.[23] Even in high-income countries the prevalence of smoking in various regions within the United States of America before, during and after pregnancy varied widely with smoking prevalence during pregnancy ranging from 2 - 30%. Overall smoking prevalence was highest in the 3 months preceding pregnancy (almost 25%), decreasing during pregnancy (12.3%) and after pregnancy (17.2%), however tobacco-control efforts have achieved minimal reductions and much higher than national objectives of smoking within pregnancy (1.4%).[21]

3.3 ETS exposure and respiratory tract infection in children

Respiratory tract infections (RTI) associated with ETS exposure include upper RTI (otitis

media, sinusitis, pharyngitis, tonsillitis) and lower respiratory tract infections (LRTI).[24] An increased risk of 1.2-1.6 of upper respiratory tract infection (URTI) or LRTI has been reported particularly in pre-school children exposed to parental smoking.[25] When considering the impact of prenatal versus postnatal exposure on respiratory disease, postnatal paternal smoking is associated with increased otitis media while maternal smoking in pregnancy is associated with an increase in wheezing (odds ratio (OR) 1.41, 95% CI 0.99– 2.01) or chestiness (OR 1.46, 95% CI 1.03–2.01) in the first year of life.[26] ETS is postulated to increase the risk of RTI by direct toxic effects on the mucosa, impaired ciliary function and impaired local immune defences resulting in prolonged inflammation, congestion or predisposition to infection.[27, 28]

3.3.1 Upper respiratory tract infection (URTI) (Table 2)

ETS exposure is associated with recurrent otitis media and the increased need for tympanostomy tube placement with parental smoking reported to double the risk of recurrent acute otitis media.[29, 30] Maternal smoking increased the risk of middle ear disease and the need for surgery (OR 1.86, 95% CI 1.31-2.63).[31] Exposure to ETS was more common in children undergoing tonsillectomy for recurrent tonsillitis compared to a control group who underwent hernia repair surgery.[32] Children whose parents limited their exposure to ETS by enforcing smoke-free home environments experienced fewer URTIs and decreased health-care facility visits.[30, 33]

3.3.2 Lower respiratory tract infection (LRTI) (Table 3)

ETS exposure is reported as an important risk factor for childhood LRTI in several studies.[2] An updated systematic review found smoking by either parent (OR 1.22, 95% CI 1.10-1.35) both parents (OR 1.62, 95% CI 1.38-1.89) or a household member (OR 1.54, 95% CI 1.40-1.69) significantly increased the risk of LRTI.[34]

In children hospitalised for community-acquired pneumonia, household ETS exposure was found to increase length of hospital stay and severity of pneumonia, particularly with more than two smokers in a household. [35] In a Canadian study, ETS exposure was also associated with severe LRTI in the first 2 years of life, predisposing to further respiratory morbidity in pre-school years.[36] Other studies, from LMICs have also shown this

association.[37, 38, 39] A high incidence of pneumonia [0.27 episodes per child-year (95% CI 0.23-0.32)] was reported in infants in the Drakenstein Child Health study, an African birth cohort study; maternal smoking was strongly associated with pneumonia (RR 2.36, 95% CI 1.45-3.82).[37] Studies from Nepal and Indonesia confirm a similar risk,[38, 39] and in a large questionnaire based study from Taiwan, prenatal ETS exposure or maternal smoking were significant risk factors for infantile pneumonia.[40] A Vietnamese study of almost 25 000 children less than 5 years of age, found that household ETS exposure to be independently associated with hospitalisation for pneumonia (adjusted OR 1.55, 95% CI 1.25-1.92). [41]

Bronchiolitis is a major cause of respiratory morbidity in young children and while ETS exposure is a recognised risk factor, the source and timing of exposure varies. A systematic review found that post-natal maternal smoking was strongly associated with bronchiolitis (OR 2.51, 95% CI 1.58 - 3.97).[34] More recently prenatal ETS exposure and heavy postnatal maternal smoking were both associated with an increased risk of hospitalization for bronchiolitis in the first year of life; however post-natal exposure increased the risk by 2 fold compared to prenatal ETS exposure.[42] Further, both prenatal and postnatal maternal smoking were associated with an increased risk for admission to intensive care (ICU): OR = 1.51 (95% CI 1.14–2.00) for prenatal and OR = 1.95 (95% CI 1.13–3.37) for postnatal exposure. [43]

3.3.3 Pathogen specific disease (Table 4)

Respiratory Syncytial Virus (RSV) is a leading cause of acute respiratory disease in children and may cause severe disease. ETS has been found to increase the risk of severe RSV disease as measured by hospitalisation and hypoxia in both infants and children (adjusted OR 2.2 – 3.8).[44] A recent systematic review and meta-analysis identifying risk factors for RSV-associated LRTI in children reported maternal smoking to be one of the most important risk factors (OR 1.36, 95% CI 1.24–1.50). [45]

Severe influenza virus disease has also been associated with ETS exposure, with ETS exposure associated with a 20% increased need for ICU admission and 12% increased risk of intubation compared to children without ETS exposure.[46]

Pneumococcal nasopharyngeal carriage has also been associated with smoke exposure in Australian children [47]. However, in a systematic review of the association between ETS exposure and invasive bacterial disease, this association only occurred with meningococcal disease. [48] Another systematic review on the health effects of passive smoking also reported an increased risk for invasive meningococcal disease, pneumococcal carriage and LRTI in children.[49]

Tuberculosis (TB) remains a global health problem with young children particularly vulnerable to developing disease especially those living in LMICs. Studies from high burden TB regions demonstrate an association between ETS exposure and development of TB disease in adults.[50, 51] While the effects of tobacco smoking and exposure on TB have been well described in adults, there are fewer studies focusing on children. A systematic review and meta-analysis found that ETS exposure caused both an increase in TB infection (OR 1.9, 95% CI 0.9–2.9) and disease (OR 2.8, 95% CI 0.9–4.8) in children. [52]

3.4 ETS exposure and chronic lung disease in children

3.4.1 Asthma

Childhood asthma is the commonest non-communicable disease in children.[53] Findings from the International Study of Asthma and Allergies in Childhood (ISAAC) have confirmed the association between maternal smoking, and symptoms of asthma or rhinoconjuctivitis with an additive risk being paternal smoking.[3] Increasing number of maternal cigarettes smoked was associated with a higher prevalence of asthma symptoms. Further, maternal smoking in the first year of a child's life was associated with a greater risk of all asthma symptoms at 13 to 14 years, highlighting the impact of early exposure on long-term respiratory outcome.[3] ETS exposure has also been associated with more severe asthma attacks; children with asthma and ETS exposure were twice as likely to be hospitalised for asthma and had more emergency unit visits (OR 1.66, 95% CI 1.02-2.69) than unexposed asthmatics.[54] A 20% increased length of hospital stay was also found in ETS exposed asthmatic children.[55] ETS exposure also impacts on asthma control with decreased response to inhaled corticosteroids and impaired histone deacetylase-2 function, possibly contributing to steroid resistance in asthmatic children.[56] In utero to-

bacco smoke exposure increased age-related airway hyperresponsiveness and reduced the efficacy of inhaled corticosteroids in asthmatic children.[57] Further, increased passive smoke exposure, as quantified by measuring urine cotinine, was also associated with more severe asthma exacerbations in Iranian children.[58] ETS exposed children had increased co-morbid conditions with significantly higher body mass index percentiles (>75%, OR 1.64, 95% CI 1.22-2.2) and were more likely to have more severe asthma then non-exposed controls.[59]

In a recent meta-analysis, comparing antenatal and postnatal smoke exposure on the incidence of asthma and wheeze, children exposed to either antenatal or postnatal tobacco smoke exposure had a 30-80% increased risk of developing wheezing and a 21-85% increased risk of developing asthma.[60] However the strongest risk for the development of wheezing was in children under 2 years with postnatal tobacco smoke exposure (OR 1.70, 95% CI 1.24–2.35) while the risk of developing asthma was associated with antenatal maternal smoking (OR 1.85, 95% CI 1.35–2.53).[60] By contrast in a large population-based prospective cohort study, continued maternal smoking during pregnancy led to increased risk of early and persistent wheezing (OR 1.24, 95% CI 1.01-1.52; OR 1.48, 95% CI 1.13-1.95) and asthma (OR 1.65, 95% CI 1.07-2.55).[61] Post-natal paternal smoking was however not associated with an increased risk of wheezing.[61]

This was confirmed in a recent meta-analysis focusing on smoke exposure and the development of wheezing and asthma in unselected birth cohorts. This analysis found a 36% increased risk of wheezing in early-life of infants whose mothers' smoked during pregnancy, while no clear exclusive post-natal effect could be demonstrated.[62] While maternal smoking and exposure increase the risk of asthma development, in non-smoking mothers antenatal maternal ETS exposure also increased the risk of asthma development in their children.[63]

3.4.2 Chronic obstructive pulmonary disease (COPD)

One of the first studies to explore the association between ETS exposure in childhood and the development of COPD in adulthood found an almost 2-fold increased risk of women developing COPD following childhood ETS exposure. There was also an increased risk of

COPD symptoms in men exposed to ETS in childhood compared to those unexposed.[64]

Follow-up of participants from the Tucson Children's Respiratory birth cohort study through first 26 years of life has demonstrated that ETS exposure in utero and during early-life increases the susceptibility to the harmful effects of active smoking in early adulthood and an accelerated decline in lung function.[65]

A number of studies have reported the impact of early-life smoke exposure on the "genetic programming" that control life-long lung development and aging with consequent susceptibility to obstructive lung diseases.[66] Studies investigating genetic determinants of obstructive lung disease and the effect of early life smoke exposure on gene expression, have found at least 3 COPD genes whose expression may be influenced by in utero tobacco smoke exposure.[67, 68] Epigenetic changes may account for such generational effects.[69] Mice models show alterations in DNA methylation and airway hyperreactivity in response to in utero ETS.[70] Recent human studies have also found smoke exposure specific blood DNA methylation changes present in pre-school children, which were comparable to those found at birth.[71] DNA methylation changes following in utero tobacco smoke exposure were also found in foetal lung and placental tissue suggesting a foetal origin for chronic diseases in later life.[72]

3.4.3 Bronchopulmonary Dysplasia (BPD)

While there is limited data on ETS exposure and BPD, the association between antenatal ETS exposure and preterm delivery is well recognized and there is a strong association between preterm delivery and bronchopulmonary dysplasia (BPD).[73] Gestational exposure of mice to cigarette smoke resulted in alveolar simplification and induction of a BPD-like condition in their offspring. This was mediated by down regulation of nicotinic receptors that in turn regulate other factors (hypoxia-inducible factor-1) involved in apoptosis control and angiogenesis in the developing foetal lung, which may explain the effects of ETS exposure on BPD.[74] In very low birth weight infants, intrauterine smoke exposure was also found to be an independent risk factor for BPD (OR 2.21; 95% CI 1.03-4.76).[75] More recently a case-control study looking at the respiratory outcomes of preterm infants with and without BPD exposed to both in utero smoking (IUS) and post

natal ETS showed that infants with BPD on home oxygen had the highest exposure to both.[76] Chronic tobacco smoke exposure as assessed by hair nicotine levels was common in children with BPD; relying on caregiver reported smoke exposure underestimated this by almost 50%. Further, in children who required respiratory support (home oxygen or ventilation) higher log hair nicotine levels were associated with increased hospitalisations and limitation of activities.[77]

3.4.4 Cystic Fibrosis (CF)

The deleterious effects of ETS exposure are likely to be more pronounced in children with chronic respiratory conditions including cystic fibrosis (CF).[78] One of the few studies to look at the effects of ETS exposure in infants with CF found diminished growth as measured by length and weight/length at 4 and 12 months of age in smoke exposed CF infants as compared to unexposed CF infants. Exposed CF infants also had increased air trapping (measured on CT scan), bronchodilator responsiveness (4.2-fold increase) and a higher prevalence of methicillin resistant *S. aureus* and anaerobes on respiratory cultures.[79] In utero tobacco smoke exposure was also found to precipitate earlier structural lung disease in young CF children with increased CT scan diagnosed bronchiectasis (1.45 CF-CT score points [95% CI 0.35 – 2.56]) and air-trapping (1.39 CF-CT score points [95% CI 0.13 – 2.63]) as well as a shorter time to first infection. ETS exposed CF children also had decreased forced expiratory volumes (FEV1) at 6 years of age. These effects were strongest for maternal smoking; paternal smoking during gestation had a similar but milder effect.[80] The significant effects of maternal smoking on lower lung function in young CF patients warrants smoking cessation strategies targeting parents of this vulnerable group of children. Telephonic counseling and trained nurse led interventions were found to be effective in enabling parents of children with CF to reduce or quit smoking in 12.5% of participants.[81]

Both in-vitro and in-vivo studies have shown that cigarette smoke decreases the expression of cystic fibrosis transmembrane regulator (CFTR) gene, protein and function contributing to the pathophysiology of existing CFTR deficiencies.[82]

3.5 ETS exposure and lung function

The detrimental effects of ETS exposure on lung function have been well documented.[11, 83] ETS exposure in children is associated with lower forced expiratory volume (FEV1) values compared to matched unexposed children.[84] Antenatal maternal smoking has been associated with a reduction in early-life lung function suggesting in utero smoke exposure may affect airway development and lung elasticity.[85] Maternal smoking during pregnancy and in early life is the most significant source of exposure affecting infant lung function.[83]

Changes in infant lung function due to antenatal or early postnatal ETS can be detected very early in infants. In a South African birth cohort, the Drakenstein child health study, maternal smoking in pregnancy or postnatally was associated with a 19% lower compliance in exposed compared to unexposed infants at 6 weeks of age as measured by the forced oscillation technique.[86] In a large Chinese study of ETS exposure in pre-school children, ETS exposure, as quantified by urine cotinine levels, was a significant risk factor for lung function impairment measured by spirometry.[87]

Longitudinal cohort studies have shown that lung function trajectories are set in early life with a developmental window of susceptibility, which can be disrupted by both infectious and environmental exposures.[10, 88, 89] Maternal smoking reduces infant lung function which is associated with impaired lung volume in adulthood (both for FEV1 and forced vital capacity [FVC]), independent of smoking in adulthood, compounding the effect of smoking to reduce airflow limitation and increasing the risk of COPD.[90] Parental smoking was also responsible for a rapid decline in FEV1:FVC ratio in young adulthood even more (3%) than that of smokers not exposed to parental smoke.[65] The majority of studies focused on air flow limitation (FEV1 and FEV1:FVC) as a marker of ETS exposure related airway obstruction.[90]

Even low levels of ETS exposure have been shown to affect lung function in pre-school asthmatic children.[91] Further, ETS may increase airway inflammation in young children. ETS exposed steroid naïve pre-school wheezers were found to have higher levels of exhaled nitric oxide (FeNO) and higher respiratory resistance, as measured by impulse oscillometary, compared to unexposed children. [92]

3.6 The additive effect of indoor air pollution (IAP) and ETS exposure on lung health in children

The use of alternate fuel sources for cooking and heating is an important contributor to indoor air pollution (IAP) particularly in LMIC. [93] The multiplicative effects of air pollution, from both indoor and outdoor sources and ETS exposures are important particularly as these countries carry the highest burden of child respiratory diseases. [94] ETS combined with other IAP particularly antenatal exposure affects lung growth that persists through adulthood.[95] There are numerous by-products of combustion; particulate matter (PM), carbon dioxide (CO_2), sulphur dioxide (SO_2), nitrogen dioxide (NO_2) and volatile organic compounds (VOC) are the most commonly assessed by-products of both ETS and other combustions.[93, 96] Recently it has been shown that sub- and nano-micron particles contribute to adverse effect of particulate matter on the lung health of children.[97] A South African birth cohort study that evaluated the home environment and measured IAP in a peri-urban setting, reported high passive tobacco smoke exposure (44%) and benzene (VOC) levels (median 5.6 µg/m3 [IQR 2.6– 17.1]) exceeding acceptable ambient standards. Significant associations between fossil fuel use and increased benzene [OR 3.4 (95% CI 2.1–5.4)], carbon monoxide [OR 2.9 (95% CI 1.7–5.0)] and nitrogen dioxide [OR 18.6 (95% CI 3.9–88.9)] levels were also found.[98] In an Italian study that examined the association between household cohabitants' smoking behaviours and urinary cotinine and benzene (a tobacco-related carcinogen) levels in children contacts, found the levels of urinary benzene paralleled that of urine cotinine and were related to smoking behaviours such as smoking indoors vs outside the home.[99] Adverse respiratory outcomes are associated with a number of combustion by-products. A Chinese study of over 3000 preschool children showed that gestational and early life exposure to NO_2 from ambient air pollution was associated with asthma (OR 1.77; 95% CI 1.29–2.43) or allergic rhinitis (OR 1.67; 95% CI: 1.07–2.61).[100] Indoor exposure to particulate matter ($PM_{2.5}$) above levels of 100ug/m^3 was independently associated with younger age of first LRTI [12% decrease (95% CI 2 – 21) in age] in Bangladeshi children.[101] Another African study assessing the effects of pollution from ETS, cooking and heating fuels and outdoor traffic found an increased risk of wheezing from both indoor and outdoor air pollution sources. ETS exposure at home was associated with current wheeze (OR 1.36 95% CI: 1.06 − 1.77); use of gas for residential heating was

associated with wheeze ever (OR 1.68 95% CI: 1.23 − 2.28) or current wheeze (OR 1.61 95% CI: 1.08 − 2.39); paraffin most frequently used for residential heating was associated with current severe wheeze (OR 1.85 95% CI: 1.04 − 3.28).[102] The risk of LRTI mortality in LMIC is also increased by environmental exposures including ETS (OR1.52, 95% CI 1.20 - 1.93) or IAP (OR 3.02, 95% CI 2.11–4.31).[103]

3.7 Prevention of exposure to ETS

The long term burden of ETS exposure on respiratory morbidity and mortality is substantial. Public health programmes that highlight not only the acute effects of ETS but also the long-term consequences on child health are needed. In utero and early-life ETS exposure remains an important risk factor for respiratory disease in young children with consequent long-term effects on respiratory health. Increasing evidence indicates that the roots of adult COPD lie in antenatal and early life exposures including ETS.[104] The generational effect of smoke exposure are important with evidence emerging of maternal smoking in pregnancy impacting on subsequent risk of asthma in grandchildren regardless of the mother's smoking status or of long term COPD.[105]

Global attempts to curb the tobacco epidemic include the World Health Organisation's tobacco-free initiative, aimed at implementing smoke-free environments and legislation limiting tobacco advertising, particularly to prevent initiation of tobacco and nicotine addiction among youth.[5, 106, 107] While these measures aim to control tobacco smoke exposure in public places, household exposure remains problematic. Public health interventions require measures that target the tobacco industry through taxes on cigarette sales and warnings on cigarette packets but should also include local community involvement to ensure culturally acceptable interventions particularly in LMIC.[108]

Key preventative strategies to protect children from tobacco smoke and nicotine exposure include a comprehensive ban on tobacco smoke, ban of smoking in multi-house units and the ban on the use of nicotine delivery systems (e-cigarettes).[104]

It is essential that counselling and smoking cessation programs are offered to parents to address parental dependency and to reduce the impact of early life exposures pre-con-

ception, to promote child health and prevent long-term sequelae.[104, 109] Effective smoking cessation programmes targeting vulnerable groups, especially women, pregnant women and adolescents, particularly in LMICs are required to stem the smoking pandemic. A combination of motivational counselling, therapy and pharmacological therapy is usually required. Interesting, but yet unproven interventions might be using pharmacotherapy (bupropion and varenicline) and nicotine replacement therapy during pregnancy to reduce intra-uterine acquired lung disease.[110, 111]

However, the safety of pharmacological treatments in pregnant women is not established and alternative strategies including an individualised plan may be necessary.[112, 113] Further research is required in these preventative strategies in pregnant mothers.

In low middle income countries, environmental tobacco smoke and indoor air pollution are often found in the same households necessitating interventions which would benefit both exposures. Interventions that have been implemented to reduce household ETS or IAP include a combination of counselling, the installation of clean chimneys and improved ventilation in the homes of smokers. A systematic review and meta-analysis of the effectiveness of interventions to reduce ETS in homes as assessed by reduction in nicotine and PM levels, found that although some benefits were documented, at follow-up exposure was still present.[114] ETS exposure, as measured by cotinine levels, was consistently higher in children who lived in multiunit or attached housing compared to children living in detached homes, even if there were no smokers within the home.[115] Regulations to enforce smoke-free multiunit housing is a feasible intervention, particularly for new developments [114, 116] that should be considered in LMIC regions especially where government subsidised housing may be provided. However, in LMIC these interventions might not always be possible.

A novel strategy may be vitamin C supplementation to pregnant smokers who are unable to terminate smoking. A randomised double-blind trial showed that supplemental vitamin C improved newborn pulmonary function and decreased wheezing in the first year of life in infants of mothers who smoked.[117] While prevention or avoidance of smoking should be the optimal strategy in pregnancy and postnatally, this intervention needs to be further

studied in pregnant mothers who are unable to refrain from smoking in pregnancy.

Electronic nicotine delivery systems (e-cigarettes) were designed to deliver nicotine without tobacco combustion and are used in smoking cessation; however, until recently were unregulated by the Food and Drug Administration (FDA).[118,119] While e-cigarettes are marketed as a safer alternative to tobacco smoking, they contain nicotine and flavourants and the long-term effects are unknown. Nicotine is a highly active chemical that affects many bodily cells and pathways and has both activating and desensitising effects on receptors with a high risk of lethal poisoning when accidentally consumed orally by young children.[120] The attractive flavouring and active marketing of e-cigarettes also makes them appealing to the youth. Reducing tobacco use through campaigns that depict cigarette smoking as undesirable and harmful have been implemented, however, the promotion of e-cigarettes threatens this with the risk of increasing nicotine addiction.[120] A recent systematic review also found no strong evidence for e-cigarettes as a smoking cessation tool.[121] Urgent legislation and regulation of e-cigarettes is required to prevent another form of nicotine addiction targeted at vulnerable groups. [122]

4 Conclusion

Children and adolescents remain the most vulnerable groups for both ETS exposure and initiation of cigarette smoking. Parental and family education to provide a smoke free environment is vital to address this challenge.[123] Failure to do so will allow the considerable morbidly of exposure to tobacco smoke in children and adults to continue.

5 Expert Commentary

Childhood ETS exposure is an often under-recognised and reported problem particularly in LMIC where the burden of respiratory diseases is highest. ETS is associated with upper and lower respiratory disease including infections, wheezing and chronic lung disease. Exposure antenatally may represent a particularly important period that affects lung development, with intergenerational effects. The increase in the incidence of women smokers in LMIC is of concern. Effective intervention strategies to combat the increasing exposure to ETS in LMIC are urgently needed, particularly for vulnerable populations such as ad-

olescents and women of child-bearing age. However, tobacco control measures may be influenced by lobbyists and tobacco companies making regulation or legislation required to effectively implement nation-wide smoking cessation interventions difficult.

Pneumonia remains the leading cause of childhood mortality outside the neonatal period, in LMIC. ETS exposure is strongly associated with an increased risk for pneumonia and of severe disease. Further antenatal ETS is associated with childhood wheezing illness, asthma, more severe asthma attacks and reduced lung function. With lung health trajectories set in this critical development period, interventions that target smoking cessation need to be broadened to include reducing not just maternal smoking but also ETS exposure from household contacts as differentiating prenatal from postnatal exposures as risk factors is difficult.

Interventions to reduce tobacco smoke pollution within homes have shown that individual-level programmes are not effective enough to reduce contamination. Environmental risk factors from both ETS and other indoor air pollution (IAP) exposure are potentially modifiable. However, addressing these requires both population-wide smoking cessation programmes, as well as interventions to improve ventilation and decrease IAP, which may be difficult in LMIC where poverty results in poor infrastructure and high levels of air pollution within homes. In addition to the well-known exacerbating effect of poor ventilation on primary and second-hand smoking, impaired ventilation is a key factor in third-hand smoke exposure. Third-hand smoke describes pollutants than remain after the initial smoking event and react with other compounds to create secondary pollutants. These pollutants, such as carcinogenic nitrosamines, increase the risk of respiratory and non-respiratory diseases.

Electronic cigarettes provide a new risk for potential respiratory complications. This inconsistently regulated industry poses a hazard both from the often unknown constituents of the inhaled aerosol to the long-term complications associated with the use of such devices. The regulation of electronic cigarettes varies widely across different countries – from those having no specific regulation, to those who legislate it under pharmaceutical products, through to countries in which e-cigarettes are banned. While electronic

cigarettes eliminate the by-products of tobacco combustion, the nicotine inhaled may still lead to significant problems. Currently the effects of nicotine on the developing lung have mainly been studied in animal models with deleterious effects. Although passive vapour is considered safer than passive tobacco smoke exposure, the specific effects and safety levels are still being investigated. Systematic reviews on e-cigarettes have identified that some of the studies have methodological problems and / or are written by authors with conflicts of interest. Therefore, the effects of nicotine exposure on human developing lungs is a research field that requires further exploration, as the potential harm from this may be substantial.

The early-life origins of adult chronic respiratory diseases are also increasingly recognised, however the evidence from LMIC, particularly African countries is lacking. Longitudinal studies, including birth cohort studies from these regions[23, 86] may provide further insights. Collaboration between paediatric and adult health care providers can only enhance patient care by early identification and monitoring of at-risk individuals.

Certain interventions, such as antenatal vitamin C supplementation, parental enforcement of smoke-free environments, and nurse-led or telephonic support in smoking cessation, have shown positive results in reducing respiratory disease in children. These relatively simple, cost-effective interventions should therefore be widely implemented, with ongoing monitoring to confirm effectiveness.

The body of evidence confirming the association between environmental tobacco smoke exposure and childhood respiratory disease is substantial and unequivocal. Further research has the potential to identify specific underlying factors that contribute to ETS and IAP, as well as individual risk factors in children. The overall goal would be to develop targeted, cost-effective measures which would result in a tangible impact on both childhood and chronic adult respiratory diseases.

6 Five-year view

Effective anti-tobacco campaigns have to some extent reduced smoking prevalence in high income countries leaving LMIC more vulnerable to the tobacco industry. The con-

sequent health effects needs further exploration particularly as LMIC tend to face a multitude of environmental challenges.

The long-term effects of electronic cigarettes both from use and exposure will become more evident. This may contribute to better regulation of both the manufacture and distribution of these products, and will hopefully result in more consistent legislation and enforcement across countries.

With the move towards personalised medicine, epigenetic factors may play a role in identifying tailored interventions for specific groups. Furthermore, the Genetic Test to Stop Smoking (GeTSS) trial has been developed to assess if the presence of a gene associated with lung cancer may be a motivating factor in smoking cessation. In the future, genetic factors are likely to play a role both in modifying risk factors and developing novel treatment approaches to ETS-related respiratory disease.

Further research into these factors may enhance our understanding of the association between ETS exposure and childhood respiratory disease.

7 Key issues

- Global estimates of childhood environmental tobacco smoke (ETS) exposure are high (between 40-70%).
- Early life ETS exposure affects both lung development and subsequent respiratory disease, with the origins of certain adult chronic respiratory conditions beginning in childhood.
- Lifelong lung function trajectories are influenced by both prenatal and postnatal ETS exposures.
- Prevention of ETS exposure in childhood requires effective interventions to improve child and consequent adult respiratory health.

Figure 1 Flow diagram of literature review [18]

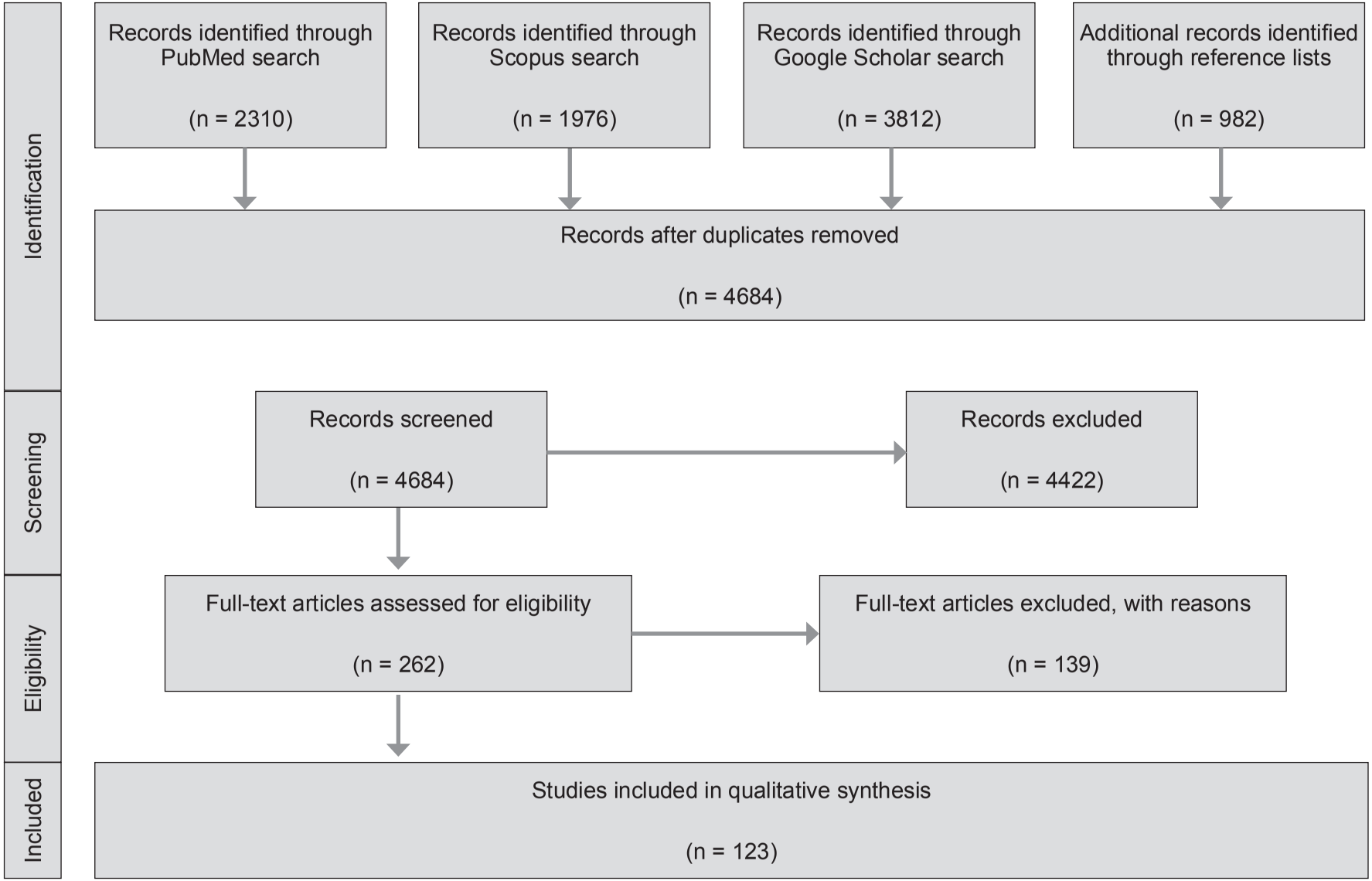

Table 1 Tobacco smoke exposure prevalence by WHO region [6, 20, 106, 108]

WHO region and sub-region*		Exposure to second hand smoke		Active smoker	
		Children <15 years (%)	Women (%)	Women (%)	Pregnant women in low and middle-income countries (%)
Africa	*D*	13	11	3	0.0 – 4.5
	E	13	9		0.0 – 5.4
The Americas	*A*	25	15	16	No data
	B	29	22		0.7 – 3.5
	D	22	19		1.0 – 4.1
Eastern Mediterranean	*B*	37	25	4	6.8 – 13.4
	D	34	35		0.4 – 3.8
Europe	*A*	51	32	22	No data
	B	61	54		0.1 – 15.0
	C	61	66		0.8 – 3.9
Southeast Asia	*B*	53	56	5	0.4 – 1.4
	D	36	19		1.0 – 5.9
Western Pacific	*A*	51	54	4	No data
	B	68	51		2.4 – 3.4
Worldwide		41	35	8	0.9 – 1.8

* WHO region and subregional grouping, based on 2004 data. Categorisation as follows: A = very low child mortality and very low adult mortality; B = low child mortality and low adult mortality; C = low child mortality and high adult mortality; D = high child mortality and high adult mortality; E = high child mortality and very high adult mortality. Adapted from WHO. [106]

Table 2 ETS exposure and upper respiratory tract infection (URTI)

First Author and Year of Publication	Type and Length of Study	Sample Size	Country and Setting	Age of Participants	Measurement of ETS Exposure	Findings
Csákánya Z, 2012. [29]	Cross-sectional, retrospective survey; 24 months	412	Hungary; paediatric hospital	6 months – 18 years	Caregiver-reported ETS exposure	ETS exposure doubled risk of recurrent acute otitis media (OR 2.03, 95% CI 0.99-4.14), increased conductive hearing loss and need for surgery.
Jones LL, 2012. [31]	Systematic review and meta-analysis	61 studies				Maternal smoking increased the risk of middle ear disease surgery (OR 1.86, 95% CI 1.31-2.63).
Straight CE, 2015. [32]	Retrospective case-control study; 39 months	497	USA; hospital records	<15 years	Documented ETS exposure from household contacts	Exposure to ETS more common in children undergoing tonsillectomy (OR 2.49, 95% CI 1.5–4.11).
Spangler J, 2014. [33]	Cross-sectional survey	208	Hungary; paediatric hospital	6 months – 18 years	Caregiver-reported ETS exposure	Limiting ETS exposure resulted in fewer URTI symptoms, health-care facility visits and adenoidectomy procedures (OR 3.2, 95% CI 1.43-6.38).

Table 3 ETS exposure and lower respiratory tract infection (LRTI)

First Author and Year of Publication	Type and Length of Study	Sample Size	Country and Setting	Age of Participants	Measurement of ETS Exposure	Findings
Jones LL, 2011. [34]	Systematic review and meta-analysis	60 studies		<2 years		Post-natal maternal smoking strongly associated with bronchiolitis (OR 2.51, 95% CI 1.58 to 3.97). Smoking by either parent (OR 1.22, 95% CI 1.10-1.35), both parents (OR 1.62, 95% CI 1.38 -1.89) or household member (OR 1.54, 95% CI 1.40-1.69) increased risk of LRTI.
Ahn A, 2015. [35]	Prospective surveillance study; 30 months	2 219	USA; paediatric hospitals	<18 years	Caregiver-reported ETS exposure	ETS exposure increased hospital stay (hazard ratio 0.85, 95% CI 0.75-0.97) and severity of pneumonia, particularly with > 2 household smokers.
Kovesi TA, 2011. [36]	Cross-sectional survey	388	Canada; community survey	3 – 5 years	Caregiver-reported ETS exposure	ETS exposure associated with severe LRTI in first 2 years (OR=6.18 for bronchitis, OR=14.6 for pneumonia); which then predisposed to increased respiratory morbidity in pre-school years.
le Roux D, 2015. [37]	Prospective cohort study; 24 months	697	South Africa; peri-urban community clinic	<1 year	Self-reported maternal smoking	High incidence of pneumonia - 0.27 episodes per child-year (95% CI 0.23-0.32); maternal smoking a significant risk factor (incidence rate ratio 2.36, 95% CI 1.45-3.82).
Shibata T, 2014. [38]	Cross-sectional survey and case-control study	461	Indonesia; urban community	<12 years	Caregiver-reported indoor air pollution exposure and particle counter measurement.	Acute respiratory infections in childhood associated with maternal ETS exposure (OR=2.05; p=0.08) and household particulate matter levels.
Karki S, 2014. [39]	Case-control study; 12 months	200	Nepal; hospital	<5 years	Caregiver-reported ETS exposure	An increasing trend between both parents smoking and childhood pneumonia (OR 2.21, 95% CI 0.56-8.82).

First Author and Year of Publication	Type and Length of Study	Sample Size	Country and Setting	Age of Participants	Measurement of ETS Exposure	Findings
Chen CH, 2012. [40]	Prospective cohort survey; 24 months	21 248	Taiwan; stratified community survey	<6 months	Caregiver-reported ETS exposure	Prenatal ETS exposure (OR 1.7, 95% CI 1.06-2.69) and maternal smoking (OR 2.43, 95% CI 1.16-4.72) significant risk factors for infantile pneumonia.
Suzuki M, 2009. [41]	Cross-sectional survey	24 781	Vietnam; community survey	<5 years	Caregiver-reported ETS exposure	Household ETS exposure (70.5%) associated with hospital admissions for pneumonia (OR 1.55, 95% CI 1.25 to 1.92).
Lanari M, 2015. [42]	Longitudinal cohort study; 38 months	2 210	Italy; neonatology units	Neonates (≥33 weeks gestation)	Caregiver-reported in utero smoke (IUS) and ETS exposure	Prenatal ETS exposure increased risk of hospitalization for bronchiolitis (hazard ratio 3.5, 95% CI 1.5-8.1). Post-natal heavy smoking doubled this risk.
Stevenson MD, 2015. [43]	Prospective cohort study; 29 months	2 207	USA; urban paediatric hospitals	<2 years	Caregiver-reported IUS and ETS exposure	Prenatal and maternal smoking and postnatal ETS increased the risk for ICU admission in children hospitalised for bronchiolitis (OR 1.95, 95% CI 1.13–3.37).

Table 4: ETS exposure and pathogen specific disease

First Author and Year of Publication	Type and Length of Study	Sample Size	Country and Setting	Age of Participants	Measurement of ETS Exposure	Findings
DiFranza JR, 2012. [44]	Systematic review	30 studies		<5 years		ETS increases risk of severe RSV disease as measured by hospitalisation and hypoxia (adjusted OR = 2.2–3.8).
Shi T, 2015. [45]	Systematic review and meta-analysis	20 studies		< 5 years		Maternal smoking is a significant risk factor for RSV-associated acute LRTI in children (OR 1.36, 95% CI 1.24-1.50).
Wilson KM, 2013. [46]	Retrospective cohort study; 7 years	117	USA; urban paediatric hospital	≤15 years	Documented ETS exposure from household contacts	Children with an influenza virus infection and ETS exposure have a 20% increased need for ICU admission (OR 4.7, 95% CI 1.4-18.5) and are 12% more likely to be intubated (OR 8.8, 95% CI 0.9-232.4).
Mackenzie GA, 2010. [47]	Cross-sectional survey	551	Australia; rural communities	2 – 15 years	Caregiver-reported smoke exposure	Pneumococcal carriage associated with smoke exposure (OR 6.89, 95% CI 1.31-3.73).
Lee CC, 2010. [48]	Systematic review and meta-analysis	42 studies		1 month – 19 years		Association between ETS exposure and invasive meningococcal disease (OR 2.02, 95% CI 1.52-2.69).
Cao S, 2015. [49]	Overview of systematic reviews	16 reviews				Passive smoking associated with increased risk for invasive meningococcal disease (OR 2.18, 95% CI 1.63-2.92), pneumococcal carriage (OR 1.66, 95% CI 1.19-2.36) and LRTIs in infants (OR 1.42, 95% CI 1.33-1.51).
Sridhar S, 2014. [50]	Prospective cohort study	714	Turkey; community recruitment	1 month – 16 years	Caregiver-reported ETS exposure	ETS exposure associated with a significant increased risk of acquiring TB infection (OR 1.5, 95% CI 1.09-2.06).

First Author and Year of Publication	Type and Length of Study	Sample Size	Country and Setting	Age of Participants	Measurement of ETS Exposure	Findings
du Preez K, 2011. [51]	Cross-sectional study	196	South Africa; impoverished urban community	3 – 15 years	Caregiver-reported ETS exposure	Dose-response relationship between level of ETS exposure and risk of TB infection. Household member pack years associated with tuberculin skin test ≥ 15mm (OR 1.09, 95% CI 1,01-1.17).
Jafta N, 2015. [52]	Systematic review and meta-analysis	8 studies		≤15 years		ETS exposure caused both increase in TB infection (OR 1.9, 95% CI 0.9–2.9) and disease (OR 2.8, 95% CI 0.9–4.8).

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Home environment and indoor air pollution exposure in an African birth cohort study.

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5 Abstract

Background: Household indoor air pollution (IAP) is a global health problem and a risk factor for childhood respiratory disease; the leading cause of mortality in African children. This study aimed to describe the home environment and measure IAP in the Drakenstein Child Health Study (DCHS), an African birth cohort.

Methods: An antenatal home visit to assess the home environment and measure IAP (particulate matter, sulphur dioxide, nitrogen dioxide, carbon monoxide and volatile organic compounds (VOCs)) was done on pregnant women enrolled to the DCHS, in a low-socioeconomic, peri-urban South African community. Urine cotinine measured maternal tobacco smoking and exposure. Dwellings were categorised according to 6 household dimensions. Univariate and multivariate analysis explored associations between home environment, seasons and IAP levels measured.

Results: 633 home visits were completed, with IAP measured in 90% of homes. Almost a third of participants were of the lowest socio-economic status and the majority of homes (65%) lacked 2 or more of the dwelling category dimensions. Most households had electricity (92%), however, fossil fuels were still used for cooking (19%) and heating (15%) in homes. Antenatal maternal smoking prevalence was 31%; 44% had passive smoke exposure. Of IAP measured, benzene (VOC) was significantly above ambient standards with median 5.6ug/m^3 (IQR 2.6-17.1). There were significant associations between the use of fossil fuels for cooking and increased benzene [OR 3.4 (95% CI 2.1-5.4)], carbon monoxide [OR2.9 (95% CI 1.7 - 5.0)] and nitrogen dioxide [OR 18.6 (95% CI 3.9 - 88.9)] levels. A significant seasonal association was found with higher IAP levels in winter.

Conclusion: In this low-socioeconomic African community, multiple environmental factors and pollutants, with the potential to affect child health, were identified. Measurement of IAP in a resource-limited setting is feasible. Recognising and quantifying these risk factors is important in effecting public health policy changes.

1 Introduction

Household indoor air pollution (IAP) is a leading cause of morbidity and mortality globally[1] and a major risk factor for childhood respiratory disease and for severe disease.[2-4] Childhood respiratory disease, particularly pneumonia, remains the leading cause of under-5 mortality and morbidity in low- and middle-income countries (LMICs) including South Africa.[5-7]

The risk of exposure to IAP is particularly prevalent in LMICs where alternate fuels remain the main source of fuel for cooking and heating. Alternate fuel sources include solid fuels such as coal, biomass fuel such as wood, dung and crop residues and non–solid fuels like paraffin, liquefied petroleum gas. Combustion of these products produces numerous by-products which contribute to household IAP.[8] The risk of developing childhood pneumonia is almost doubled following exposure to indoor biomass fuels, as is the long-term risk of developing chronic lung disease in adulthood.[9, 10]

In South Africa, despite increased electrification of areas, up to 40% of the population still use alternate fuel sources for household activities.[11, 12] In rural areas, up to 90% of households use biomass fuels as an energy source.[11, 13] Home environmental factors such as crowding, type of cook stove, ventilation and duration of exposure are also important

contributors to exposure levels.[1, 11] The contribution of IAP exposure to the incidence and severity of childhood respiratory disease has not been well studied in an African setting. Quantifying indoor air pollution is difficult and there are few studies that measure IAP in individual homes on a large scale in this context.[1, 9, 11]

The aim of this study was to describe the home environments and measure IAP in the Drakenstein Child Health Study (DCHS), an African birth cohort study.[14] Further, we aimed to investigate the feasibility of intensive sampling in individual homes in a LMIC setting and to explore associations between home environmental factors and pollutant exposure.

2 Methods

The DCHS is located in the Drakenstein sub-district of the Western Cape, South Africa, a peri-urban area 60km outside Cape Town.[14] A prospective study to assess the home environment and household IAP exposure in participants was done from March 2011 until May 2014.

Study population and participants. This low socio-economic community accessed health care mainly in the public sector. Pregnant women were recruited from two primary health care clinics: Mbekweni (serving a predominately black African population) and Newman (serving a predominately mixed race population). Consenting pregnant women were enrolled between 20-28 weeks' gestation. Mothers completed study questionnaires and provided urine for analysis of urine cotinine as a measure of smoking and smoke exposure. Urine cotinine was measured using the IMMULITE^{R} 1000 Nicotine_Metabolite Kit (Siemens Medical Solutions Diagnostics^{R}, Glyn Rhonwy, United Kingdom). This provides a quantitative test using a competitive chemiluminescent immunoassay, which contained solid-phase beads coated with polyclonal rabbit anti-cotinine antibody.[15] Urine cotinine levels were classified as <10 ng/ml (non-smoker), 10-499 ng/ml, (passive smoker), or ≥500 ng/ml (active smoker).

Assessment of home environment and indoor air pollution (IAP) exposures. Self-reported questionnaires were administered at enrolment by trained staff. A self-reported as-

sessment of socioeconomic status (SES) adapted from the South African Stress and Health Study (SASH) was done.[16] A composite SES score was developed based on current employment status and standardised scores of educational level, household income and a composite asset index made up of access to household resources, amenities and market access categorising participants as being lowest SES, low-moderate SES, moderate-high SES or high SES.

Home visits for assessment of the home environment and measurement of IAP were done antenatally within 4 weeks of enrolment. Both primary health care clinics, Mbekweni and Newman, had a dedicated team of two environmental fieldworkers trained to undertake home visits, administer questionnaires and set up equipment for IAP measurement. Field worker training was completed under the supervision of an accredited environmental laboratory (SGS Environmental Services®). Each participant received an information leaflet reviewing the reasons for the home visit and the measures being conducted. Data were gathered on type of home, its position and size, number of inhabitants, access to basic amenities, fuels used for cooking and heating, ventilation within homes and pesticides/cleaning materials used based on validated questionnaires.[17-21] An implementation of the Alkire-Foster method, a flexible technique used to incorporate a number of dimensions of poverty or well-being, that can complement poverty assessment [22, 23] was applied to the dwelling characteristics. Six dwelling factors were used; type of home (formal versus informal), primary building material (brick or cement versus other materials), water supply (piped into dwelling or yard), toilet facilities (non communal flush), kitchen type (separate room in house) and ventilation in the kitchen area (pipe or duct to exterior). Dwellings were then categorised according to the number of dimensions lacking. This method defines a dwelling as a “poor structure” if it lacks one-third or more of the factors considered. Size of the kitchen and main living room were measured using an ultrasonic measuring tool. The position of the home in relation to the road and passing traffic was also estimated.

The most common IAP were measured (Table 1). All measurements were done in the communal/main living room, away from windows and doors, approximately 1.5 meters from the ground. Devices were left in the home for 24 hours to 2 weeks depending on the measurement (Table 1, Image 1).

Measurements processing and interpretation: Following collection, samples were stored in a refrigerator (under 8^{o}C) to maintain a cold chain and transferred weekly to an accredited environmental laboratory for analysis. Samples were batched and analyses were conducted monthly. An average concentration based on the 2-week duration in the home was obtained for sulphur dioxide/nitrogen dioxide and volatile organic compounds; 24-hour averages were obtained for particulate matter. Carbon monoxide data were downloaded to a computer and the frequency of exceedance above the hourly ambient standard was calculated. Based on the 10 minute readings, total hourly concentrations were computed using the trapezium rule. Two consecutive ten minute CO readings were used to represent parallel sides of a trapezium and the 10 minute interval to represent the distance between the parallel sides (width). The trapezium formula; half the sum of the parallel sides multiplied by the width, was then applied. The sum of six consecutive trapezia areas to represent total CO concentration in an hour was then calculated. Using this approach hourly concentrations were then determined for the entire duration of the CO device in the household.

Ethics. The study was approved by the Faculty of Health Sciences Human Research Ethics Committee of the University of Cape Town and of Stellenbosch University, and by the Western Cape Provincial Health Research committee. Written informed consent was obtained from participants at the time of enrolment.

2.1 Statistical Analysis

All data were entered into a relational database (Microsoft Access^{R}) and analysed using STATA version 12. Mann-Whitney tests were used to compare medians as well as their spread. Simple and multiple logistic regression were used to examine the associations between IAP measures and home environment characteristics. For each IAP measure exposure categories were determined following South African National Ambient Air Quality Standards.[24] The 2015 ambient air quality standard values were used with the following acceptable concentrations based on an averaging period of 1 year for each measure; PM_{10}: 40ug/m^3, SO_2: 50ug/m^3 NO_2: 40ug/m^3, benzene: 5ug/m^3. For CO, a household should not have more than 88 hours in which the CO concentration was 30mg/m^3 or above.[24] For each household, the number of hours that had an hourly CO concentration

above the ambient hourly threshold was counted and expressed as proportion of the total duration of the device in the household. A household was deemed to be exposed to CO if the actual proportion of hours with CO level of 30mg/m^3 and above exceeded 1%. Home environment and other characteristics considered for the model were based on factors that may influence IAP levels and included socioeconomic status, smoking status, dwelling categorisation, access to electricity, fossil fuel usage, number of people per sleeping room and dwelling proximity to passing traffic. Univariate analysis was done for each of the IAP measures in relation to the sociodemographic and household characteristics in order to obtain a "crude" odds ratio, All these variables were then applied to a multiple logistic regression model to obtain the adjusted odds ratio. The variables included were guided by previous literature.[1, 8, 25] Univariate analysis was used for seasonal associations with IAP. Regression diagnostics followed standard procedures.[26] All P-values and confidence intervals reported were two-sided at alpha 0.05.

3 Results

In this study period 633 mothers were enrolled, with 633 antenatal home visits completed. There was good acceptability of the placement of devices, with all mothers agreeing to placement; particulate matter (PM_{10}) results were analysed for 592 homes (94%), sulphur dioxide (SO_2) for 600 homes (95%), nitrogen dioxide (NO_2) for 598 homes (95%), carbon monoxide for 505 homes (80%) and volatile organic compounds for 579 homes (91%). Where results included are fewer than total home visits completed, this was due to missing results or damaged devices.

Demographics and Home Environment. The population were predominantly of low socioeconomic status with more than half (52%) in the lowest or low-moderate SES category. Mbekweni had a higher proportion of participants in the lowest SES bracket (37%) compared to Newman (19%), p <0.001. The median household size was 5 (IQR 3-6) people; homes in Newman had significantly more people median 5 (IQR 4-7) compared to Mbekweni median 4 (IQR 3-6), p<0.001. A median of 3 (IQR 2-4) people per sleeping room was found across both sites. (Table 2)

Most homes (65%) lacked 2 or more of the dwelling categorisation dimensions with 7% of homes lacking all 6 dimensions. This was significantly higher in Mbekweni dwellings (11%) compared to Newman (3%) homes, p<0.001. Most households (92%) had electricity, with significantly more in Newman (97%) compared to Mbekweni (88%), p <0.001. Conversely, more Mbekweni homes (28%) used fossil fuels for cooking or heating compared to Newman homes in which 10% and 2% reported using fossil fuels for cooking and heating respectively. (Table 2) The majority of Mbekweni homes were estimated to be situated less that 50m away from continuously passing trucks. (Table 2)

Thirty-one percent of mothers were active smokers, with significantly more smokers at Newman (52%) than Mbekweni (11%). A further 44% of participants were passive smokers and this was higher in the Mbekweni participants (51%) compared to Newman (37%). (Table 2)

Indoor Air Pollution. The IAP measures were not normally distributed and hence the median and inter-quartile ranges were reported. The median concentration of particulate matter (PM_{10}) measured in the homes was 33.1 (IQR 13-62.2) ug/m^3, below the ambient standard of 40 ug/m^3 with no significant difference between sites. Although the median for carbon monoxide (CO) based on the hourly average for the 24 hour period in the home was 0 ug/m^3 (IQR 0 – 24.4 ug/m^3), when measuring against ambient standards, 15% of homes had hourly CO values exceeding these. The distribution of nitrogen dioxide concentrations differed significantly between Mbekweni 8.6 ug/m^3 (IQR 3.8 -15.3 ug/m^3) and Newman 7.3 ug/m^3 (IQR 3.6 – 11.4 ug/m^3), p=0.004, however these were substantially below acceptable ambient standards (40ug/m^3). Of the volatile organic compounds, the median benzene concentration was 5.6 ug/m^3 (IQR 2.6-17.1 ug/m^3) with a significant difference in the distribution of the concentrations between the sites: Mbekweni 6.0ug/m^3 (IQR 2.9 – 27 ug/m^3) versus Newman 5.6ug/m^3 (IQR 2.3 – 11.3 ug/m^3), p=0.010, both were above the acceptable ambient standard of 5ug/m^3 (Table 3).

Benzene: In the unadjusted model, the use of fossil fuels for cooking [OR 3.4 (95% CI 2.1-5.4)] as well as the use of fossil fuels for heating [OR 3.2 (95% CI 1.9-5.5)] were significantly associated with an increased level of benzene. Conversely, the presence of

electricity in the home was significantly associated with a decrease in levels of benzene [OR 0.2 (95% CI 0.1-0.4)]. (Table 4)

Carbon Monoxide: The unadjusted model also showed significant increase in carbon monoxide levels associated with fossil fuel cooking [OR 2.9 (95% CI 1.7 - 5.0)] and heating [OR 4.0 (95%CI 2.3 - 7.1)] and an associated decrease in these levels when electricity was present [OR 0.2 (0.1 - 0.4)]. (Table 4)

Particulate matter: Compared to households that had 2 people or less per sleeping room, households with 3 or more people per sleeping room were more likely to have increased particulate matter (PM_{10}) levels [OR 2.12 (95% CI 1.22 - 3.69)].(Table 4)

Nitrogen dioxide: Having 2 or less of the dwelling category dimensions was significantly associated with increased nitrogen dioxide levels [OR 4.5 (95% CI 1.2 - 17.6)] in the un-adjusted model. There was also a significant association between the use of fossil fuels for cooking [OR 18.6 (95% CI 3.9 - 88.9) and heating [OR14.2 (95% CI 3.6 - 56.0)] and increased nitrogen dioxide levels. (Table 4)

Multivariate analysis: In the adjusted model, the presence of electricity in homes was significantly associated with a decrease in benzene [OR 0.2 (95% CI 0.1-0.6)] and CO levels [OR 0.3 (95% CI 0.1-0.7)]. The use of fossil fuels for heating was significantly associated with an increase in benzene [OR 2.0 (95% CI 1.0-4.0)] and CO levels [OR 2.3 (95% CI 1.0-5.4)]. Only the use of fossil fuels for cooking maintained a significant association with increased levels of nitrogen dioxide [OR 8.6 (95% CI 1.1-67.4)] in the adjusted model. There was no significant association between household characteristics and PM_{10} levels when adjusted. (Table 4)

A significant seasonal association with benzene and carbon monoxide levels measured was found, with benzene [OR 35.9 (95%CI 10.3 - 125.5)] and carbon monoxide [OR 2.7(95% CI 1.2 - 6.2)] levels significantly higher in winter. There were an approximately equal number of home visits done in autumn, winter and spring, with fewer in the summer months. (Table 5)

4 Discussion

In this study in a poor peri-urban, South African area, we identified a number of environmental factors which may influence child health. Many homes were lacking in dimensions and basic amenities. Despite having access to electricity, fossil fuels were used as an alternate energy source in up to 20% of homes. There was a seasonal variation in IAP levels measured with higher levels associated with the winter months. The prevalance of maternal smoking was very high as was exposure to tobacco smoke in non-smoking mothers.

Measuring IAP is difficult and most studies rely on reported exposure or extrapolation following sampling of selected homes[1, 13] with few studies from LMICs and Africa in particular.[27] However, we successfully measured IAP and by-products of combustion in the vast majority of homes (over 600) providing important data on household IAP in a peri-urban, LMIC setting. Suprisingly there was relatively little exposure to IAP with only benzene, a volatile organic compound, having a median concentration above acceptable ambient standards.[24] However, ambient standards serve as a guide to acceptable levels of pollutants with levels continually being lowered. It is therefore difficult to ascertain a clear level at which health effects are associated.[1, 2, 28] The long term effects of exposure to IAP and association with childhood respiratory disease will be longitudinally studied in the DCHS.

In categorising dwellings, we found almost two-thirds of participants lived in homes that were of an inadequate structure. Despite such poor housing and living conditions, IAP measurements were made in most homes, including measures that required devices to be left in situ for 2 weeks. The type of dwelling and home environment may impact on sources of pollutants and levels measured within the home. Factors such as a non-separate kitchen, with poor ventilation, the informal construct of the dwelling and crowding may also contribute to a higher exposure level to pollutants; as evidence of this higher exposure to PM was associated with more household members per sleeping toom.[1, 29]

Despite having access to electricity, fossil fuels were used for cooking or heating in almost a third of homes of black African mothers. The relatively high cost of electricity in South Africa[30] and that it is purchased on a pre-paid basis may influence supply and

use. The predominant fossil fuels used included paraffin, wood, gas and coal, while other biomass fuels such as animal manure or crop residues were not commonly used.[31] Fossil fuel usage was significantly associated with measured benzene, carbon monoxide and nitrogen dioxide levels, contributing to household IAP. The higher use of fossil fuels amongst black African households compared to mixed race populations may be explained by the relatively lower socio-economic status of the former.

Although we did not show any significant associations between tobacco smoke and measured IAP levels, environmental tobacco smoke remains an important contributor to IAP and a recognised source of benzene. The very high levels of maternal smoking and smoke exposure are of much concern, with potential fo several adverse health effects in mothers and children.[32] Other sources of benzene include paraffin and outdoor traffic,[28] both potentially contributing to the significantly higher levels measured in the Mbekweni community.

A limitation of this study was the duration of sampling which ranged between 24 hours to 2 weeks depending on the measure and the device used. Devices were also placed in one room and this might not fully account for IAP occurring in other areas of the home. The devices used to measure IAP (except for carbon monoxide) all gave an average concentration and therefore periods of peak exposure may have be underestimated.

The sub-optimal housing, tobacco smoking and exposure, reliance on fossil fuels for energy and the associated pollutants as a result of their use are all important public health issues that need to be addressed on a policy level. IAP is often overlooked as a significant risk factor for a number of health problems[1]; recognising and quantifying these environmental risks are instrumental to effect change.

To our knowledge, this is the first African study to comprehensively measure several possible pollutants and environmental exposures during pregnancy. This study has shown that measurement of IAP in a resource limited setting is feasible; combining this with a dwelling catergorisation may provide a novel measure for a household-exposure index.

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Table 1 Measurements of IAP

Pollutant/ Measure	Device	Duration in home	Methodology
Particulate Matter (PM_{10})	Personal Air Sampling Pump (SKC AirChek 52®)	24 hours	Gravimetrically pre-weighed filter. Weighed post sampling and concentration calculated.(33)
Carbon Monoxide (CO)	Altair® Carbon Monoxide single gas detection unit	24 hours	Electrochemical sensor detection of gas at 10 min intervals. Data downloaded from device.
Sulphur dioxide/ Nitrogen dioxide (SO_2/NO_2)	Radiello® adsorbent filters in polyethylene diffusive body	2 weeks	Chemiadsorbed on to filter. Quantified by visible spectrophotometry or ion chromatography.(34)
Volatile Organic Compounds: Benzene, Toluene, Ethyl Benzene, m,p-Xylene, o-Xylene	Markes® thermal desorption tubes	2 weeks	Analysed for BTEX using the NIOSH 2549 method.(33)

Image 1: Devices used to measure IAP

Table 2 Demographics and Home Environment

	Mbekweni (n, %)	Newman (n, %)	Total (n,%)	p value
Number of mothers	*314*	*319*	*633*	
SES quartiles				
Lowest SES	115 (37)	62 (19)	177 (28)	*p<0.001
Low-mod SES	82 (26)	73 (23)	155 (24)	
Mod-high SES	71 (23)	87 (27)	158 (25)	
High SES	46 (15)	97 (30)	143 (23)	
Household Density (median, IQR)				
Household size	4 (3-6)	5 (4-7)	5 (3-6)	*p<0.001
Persons per room	2 (1-3)	1 (1-2)	2 (1-3)	*p<0.001
Persons per sleeping room	3 (2-4)	3 (2-5)	3 (2-4)	*p<0.001
Dwelling Category (Six Category variant)				
Lacking 6 dimensions†	35 (11)	8 (3)	43 (7)	*p<0.001
Lacking 5 dimensions†	34 (11)	43 (13)	77 (12)	
Lacking 4 dimensions†	63 (20)	34 (11)	97 (15)	
Lacking 3 dimensions†	8 (3)	20 (6)	28 (4)	
Lacking 2 dimensions†	102 (32)	68 (21)	170 (27)	
Lacking 1 dimensions†	55 (18)	146 (46)	201 (32)	
Lacking 0 dimensions†	17 (5)	0 (0)	17 (3)	
Dwelling Category (Two Category variant)				
Has ≤2 dimensions†	132 (42)	85 (27)	217 (34)	*p<0.001
Has > 2 dimensions†	182 (58)	234 (73)	416 (66)	
Electricity Access	277 (88)	308 (97)	585 (92)	*p<0.001
Fossil Fuel (coal, wood, paraffin, gas) Used				
Cooking	88 (28)	32 (10)	120 (19)	*p<0.001
Heating	87 (28)	7 (2)	94 (15)	*p<0.001
Type of Stove				
Electric	265 (84)	286 (90)	551 (87)	p=0.049
Paraffin	79 (25)	3 (1)	82 (13)	*p<0.001

Gas	13 (4)	28 (9)	41 (6)	*p=0.018
Wood	2 (1)	1 (0)	3 (0)	p=0.554
Coal	2 (1)	0 (0)	2 (0)	p=0.153
Smoking Exposure				
Non smoker	107 (38)	30 (11)	137 (25)	*p<0.001
Passive Smoker	143 (51)	102 (37)	245 (44)	
Active Smoker	31 (11)	143 (52)	174 (31)	
Distance of homes from continuously passing trucks				
Less than 50 meters	200 (64)	24 (8)	224 (36)	*p<0.001
50 - 100meters	67 (21)	27 (8)	94 (15)	
100 - 200 meters	42 (13)	34 (11)	76 (12)	
200 - 500 meters	3 (1)	92 (29)	95 (15)	
More than 500 meters	0 (0)	141 (44)	141 (22)	

*Statistically significant results

†Dimensions comprise: type of home; building material; water supply; toilet facilities; kitchen type; ventilation in kitchen areas

Table 3 Pollutants Measured

	Mbekweni median (IQR)	**Newman median (IQR)**	**Total median (IQR)**	**N**	**p value**
Pollutant					
Particulate Matter (PM_{10}) ug/m^3	32.9 (15.1-60.6)	33.2 (11.9-62.8)	33.1 (13.0-62.2)	592	p=0.678
Sulphur Dioxide ug/m^3	0.0 (0.0-0.2)	0.0 (0.0-0.2)	0.0 (0.0-0.2)	600	p=0.345
Nitrogen Dioxide ug/m^3	8.6 (3.8-15.3)	7.3 (3.6-11.4)	7.9 (3.8-13.3)	598	*p=0.004
Carbon Monoxide mg/m^3 §	0.0 (0.0-29.8)	0.0 (0.0-16.1)	0.0 (0.0-24.4)	505	p=0.659
Volatile Organic Compounds					
Benzene ug/m^3	6.0 (2.9-27.0)	5.3 (2.3-11.3)	5.6 (2.6-17.1)	579	*p=0.010
Toluene ug/m^3	19.8 (9.0-48.5)	19.8 (9.8-54.4)	19.8 (9.3-53.2)	579	p=0.544
Ethyl-benzene ug/m^3	2.4 (1.0-8.7)	1.8 (0.8-6.0)	2.1 (0.9-7.2)	579	p=0.085
m,p –Xylene ug/m^3	6.1 (2.5-20.5)	5.2 (2.3-14.4)	5.8 (2.4-16.2)	579	p=0.110
o-Xylene ug/m^3	2.8 (1.2-9.6)	2.1 (1.0-5.4)	2.4 (1.1-7.0)	579	*p=0.005
	Mbekweni n(%)	Newman n(%)	Total n (%)	N	p value
Carbon Monoxide exceeding ambient standard					
Above Expected Frequency	37 (14)	40 (17)	77 (15)	505	p=0.399

* Statistically significant results

§Hourly average based on entire duration in house

Table 4 Associations between home environment variables and specific pollutants

	Benzene		**Carbon Monoxide**		**Particulate matter (PM_{10})**		**Nitrogen Dioxide**	
	(>5ug/m^3)		(1% exceedence >30ug/m^3)		(>40ug/m^3)		(>40ug/m^3)	
Variable	Unadjusted OR (95%CI)	**Adjusted OR (95%CI)**	Unadjusted OR (95%CI)	Adjusted OR (95%CI)	Unadjusted OR (95%CI)	Adjusted OR (95%CI)	Crude OR (95%CI)	Adjusted OR (95%CI)
SES quartile: High SES	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Low-mod SES	1.2 (0.7-1.9)	1.2 (0.7-2.0)	0.9 (0.4-1.8)	0.7 (0.3-1.4)	1.6 (0.8-3.1)	1.6 (0.8-3.4)	0.9 (0.1-14.7)	0.52 (0.0-9.6)
Moderate SES	1.0 (0.6-1.6)	1.1 (0.7-1.9)	0.6 (0.3-1.3)	0.5 (0.2-1.1)	1.6 (0.8-3.1)	1.8 (0.8-3.6)	1.8 (0.2-19.5)	2.5 (0.2-32.3)
Lowest SES	1.6 (1.0 - 2.6)	1.4 (0.8-2.3)	1.4 (0.7-2.6)	0.9 (0.4-2.0)	1.4 (0.7-2.8)	1.3 (0.6-2.9)	5.1 (0.6-42.8)	1.8 (0.2-20.2)
Smoking category: Not exposed	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Exposed	0.9 (0.6 - 1.4)	0.9 (0.6 - 1.4)	1.3 (0.7 - 2.4)	1.4 (0.7 - 2.6)	1.5 (0.8 - 2.6)	1.4 (0.8 - 2.5)	3.0 (0.4 - 23.5)	3.5 (0.4 - 29.6)
No Electricity	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Electricity	0.2 (0.1 -0.4)	0.2 (0.1 -0.6)	0.2 (0.1 -0.4)	0.3 (0.1 -0.7)	0.7 (0.3 -1.4)	0.4 (0.2 -1.2)	0.1 (0.0 - 0.4)	1.3 (0.2 - 7.5)
Dwelling Category: Have more than 2	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Have 2 or less	1.0 (0.7 -1.4)	0.6 (0.4 -0.9)	1.3 (0.8 -2.2)	0.7 (0.4 -1.4)	0.7 (0.5 -1.2)	0.6 (0.3 -1.0)	4.5 (1.2 - 17.6)	2.4 (0.4 - 13.8)
No fossil stove	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Fossil Stove	3.4 (2.1 -5.4)	1.5 (0.8 -3.0)	2.9 (1.7 -5.0)	1.1 (0.5 -2.6)	1.2 (0.7 -2.0)	1.1 (0.5 -2.5)	18.6 (3.9 - 88.9)	8.6 (1.1 - 67.4)
No fossil heating	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Fossil Heating	3.2 (1.9 -5.5)	2.0 (1.0 -4.0)	4.0 (2.3 -7.1)	2.3 (1.0 -5.4)	1.3 (0.7 -2.2)	1.3 (0.6 3.0)	14.2 (3.6 - 56.0)	3.2 (0.6 - 16.9)
Room density: 1-2 per room	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
More than 2 per room	1.1 (0.8 -1.5)	1.2 (0.8 -1.8)	1.1 (0.6 -1.8)	1.2 (0.7 -2.2)	2.1 (1.2 -3.7)	1.7 (1.0 -3.0)	0.5 (0.1 - 1.9)	0.5 (0.1 - 1.8)

Table 5 Seasonal association with pollutants measured

	Benzene (>5ug/m^3)	**Carbon Monoxide (1% exceedence >30ug/m^3)**	**Particulate Matter (PM_{10}) (>40ug/m^3)**
	Crude OR (95%CI)	Crude OR (95%CI)	Crude OR (95%CI)
Season			
Summer (n=103,16%)	Reference	Reference	Reference
Autumn (n=189,30%)	23.1 (6.6 - 80.9)	0.8 (0.3 - 2.0)	0.7 (0.4 - 1.5)
Winter (n=172,27%)	35.9 (10.3 - 125.5)	2.6 (1.1 - 6.0)	1.3(0.7 - 2.4)
Spring (n=169 27%)	8.3 (2.4 - 28.4)	2.7(1.2 - 6.2)	1 (0.5 – 2.0)

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Chapter 4

Antenatal and early life tobacco smoke exposure in an African birth cohort study

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Abstract

Background: Tobacco smoke exposure has not been well studied in African infants, despite the high burden of childhood respiratory disease in these communities.

Objective: To investigate the prevalence of antenatal and early life tobacco smoke exposure and associations with infant birth outcomes in an African birth cohort, the Drakenstein Child Health Study.

Methods: Self-report questionnaires assessing maternal and household smoking were administered. Maternal and infant urine cotinine testing was conducted antenatally, at birth and at 6-10 weeks of life to measure tobacco smoke exposure. Multivariate regression models explored the associations between smoke exposure and infant birth outcomes.

Results: Of 789 pregnant women included, 250 (32%) were active smokers on cotinine testing. At birth and at 6-10 weeks of life, respectively, 135/241 (56%) and 154/291 (53%) infants had urine cotinine levels indicating tobacco smoke exposure. Household smoking was prevalent and was associated with positive infant cotinine tests. Antenatal maternal smoking was associated with decreased infant birthweight-for-age z-score (0.3 (95% CI: 0.1 – 0.5).

Conclusion: Antenatal and early life tobacco smoke exposure is highly prevalent in this community, and may impact on birth outcomes and subsequent child health. Smoking cessation interventions are urgently needed to reduce tobacco smoke exposure in African communities.

1 Introduction

Tobacco smoke exposure is an important risk factor for childhood respiratory disease [1-3] and childhood morbidity and mortality worldwide.[4, 5] Prenatal exposure is associated with an increased risk of pneumonia and of wheezing disorders [6-8] and may also lead to preterm delivery and decreased birthweight, predisposing infants to severe respiratory disease.[9, 10] Similarly, other maternal socioeconomic and psychosocial risk factors, including depression and intimate partner violence (IPV), may impact on infant birth outcomes. [11-13]

Tobacco smoke exposure often begins *in utero* with maternal active or passive smoking, and may continue postnatally. Both prenatal and postnatal exposure adversely affect infant health. Nicotine exposure may be directly toxic to the airways or may result in secondary impairment of lung growth due to decreased fetal breathing or cellular damage.[14] Further, adult smokers have a higher risk of respiratory infections with increased risk of pathogen transmission to child contacts.[15]

Cotinine, a biomarker of tobacco smoking and exposure, has been used to both confirm and quantify smoking and exposure in pregnant women.[9, 16, 17] Infant exposure during the first year of life has been assessed using blood, urine or hair cotinine measures.[16, 18-20] However, no studies have used infant cotinine measurements at birth to assess *in utero* tobacco smoke exposure and few studies have used infant measures to evaluate early life exposure. [16, 18] Documenting exposure is especially relevant in low-and-middle income country (LMIC) settings, which carry the highest burden of childhood respiratory illnesses. We thus measured antenatal and early postnatal tobacco smoke exposure; and investigated the association between antenatal exposure and infant birth outcomes in an African birth cohort study.

2 Methods

A prospective study of smoke exposure was undertaken in pregnant women and infants enrolled in the Drakenstein Child Health Study.[21] The study is located 60km outside Cape Town, South Africa in a semi-rural area with a low socioeconomic population.[21] More than

90% of the population obtain health care in the public sector with a strong primary health care system.

Study population, participants and procedure. Pregnant women were consecutively enrolled using convenience sampling, between 20 and 28 weeks' gestation from one of two primary health care clinics serving different populations – Newman (predominantly mixed race) and Mbekweni (predominantly black African). A second antenatal study visit was completed at 28-32 weeks' gestation. All births occurred at a single central public hospital, Paarl Hospital. Thereafter, mother-infant dyads attended follow-up visits including at 6-10 weeks' postpartum. [21]

Self-reported measures. Sociodemographic data were collected at enrolment using a questionnaire adapted from the South African Stress and Health Study.[22] A composite socioeconomic status (SES) score was developed as an internal comparison of SES for this sample, and participants were categorised as lowest, low-moderate, moderate-high or highest SES.[13].

Maternal tobacco smoking and exposure were assessed using self-report questionnaires at enrolment. Maternal smoking was quantified as pack years, where one pack year was defined as 20 cigarettes smoked daily for one year. Maternal nicotine dependence was assessed using the Fagerström test, a well-validated questionnaire which scores tobacco dependence as low, low-moderate, moderate or high.[23]

The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) was administered to assess substance use and substance-related risk.[24] Participants were categorized as being at low, moderate, or high risk of tobacco-related health problems, and any self-reported antenatal alcohol use was documented. [24] Women who reported antenatal substance use were counselled regarding cessation.

Comprehensive psychosocial data were collected antenatally, including an assessment for depression using the Beck Depression Inventory (BDI-II) and a questionnaire for any past-year IPV. [11, 13]

Birth outcomes. All births were attended by a member of the study team. Birth outcomes included birthweight, gestational age and presence of respiratory or other disease. Gestational age at delivery (in completed weeks) was calculated from an antenatal ultrasound. If this was not available then fundal height at enrolment or maternal recall of last menstrual period was used.

Urine cotinine testing. Maternal and infant urine cotinine tests were performed using the IMMULITE^{R} 1000 Nicotine Metabolite Kit (Siemens Medical Solutions DiagnosticsR, Glyn Rhonwy, United Kingdom) [25] This provided a quantitative test using a competitive chemiluminescent immunoassay, which contained solid-phase beads coated with polyclonal rabbit anti-cotinine antibody. The test had a calibration range of 10-500 ng/ml, with an analytical sensitivity of 2 ng/ml.[25] Urine cotinine levels were classified as <10 ng/ml (non-smoker), 10-499 ng/ml, (passive smoker/exposed), or ≥500 ng/ml (active smoker) according to the manufacturer's directions.

Maternal urine was collected at the second antenatal study visit and at birth, with the higher result used to classify smoking levels. Infant urine was collected at birth and at 6-10 weeks, either via a urine bag or by placing a cotton-wool ball in the diaper from which urine could then be squeezed. Urine samples were transferred to a clean, preservative-free, plastic container and transported at temperatures between 2-8 ^{0} C to the accredited medical laboratory for testing.

Ethics. The study was approved by the Faculty of Health Sciences Human Research Ethics Committees of the University of Cape Town and of Stellenbosch University, and by the Western Cape Provincial Health Research committee. Written informed consent was obtained from mothers at enrolment.

Statistical analysis. Tobacco smoking and exposure were compared across recruitment site using x^2 or Fisher exact tests for categorical variables and Wilcoxon rank sum tests (Mann-Whitney tests) for non-normally distributed continuous variables. The sensitivity and specificity of self-reported maternal smoking was calculated, using maternal urine cotinine as the "gold standard" measure. The associations between household and maternal smoking (self-reported and based on urine cotinine) and infant urine cotinine

were assessed using x^2 tests, with cotinine levels of ≥10 used to categorize infants as exposed to tobacco smoke. Risk ratios (RR) with 95% confidence intervals (CI) were calculated to determine the strength of these associations. Infant weight-for-age (WfA) z-scores were calculated using the revised Fenton preterm growth charts and infants with a WfA z-score <10th percentile were classified as small for gestational age (SGA). [26, 27] The associations between each of maternal and infant cotinine levels, potential confounders, and infant birth outcomes were explored in regression models. Data were analyzed using Stata 12 (StataCorp Inc, College Station, Texas, USA).

3 Results

Data from 789 mothers, enrolled between March 2012 and October 2014, were included; 792 infants (including 3 sets of twins) were born, and data from 720 mother-infant dyads at 6-10 weeks' postpartum were included.

The median age of mothers at enrolment was 25.7 (IQR 21.8 – 30.8) years. A high prevalence of unemployment (74%) was observed, and most participants had not completed secondary education. Although this is a low socioeconomic population overall, the mixed race community (Newman) were of comparatively higher SES than the black African community (Mbekweni). Twenty-one percent of mothers screened above threshold for antenatal depression and almost one-third reported having experienced recent IPV. Self-reported antenatal alcohol use was significantly higher amongst mixed race (28%) compared to black African (8%) participants. (Table 1).

Maternal Smoking. Overall, 24% of mothers reported smoking antenatally. Most (94%) reported smoking daily with a median of 1.2 pack-years (IQR 0.4 -2.5). Nicotine dependence was classified as low or low-moderate in 77% of smokers. However, there was a moderate to high risk of tobacco-related problems in 97% of smoking mothers (Table 2).

Using urine cotinine, 250 (32%) mothers were classified as active smokers and 366 (46%) as having passive smoke exposure. The prevalence of both self-reported smoking and active smoking based on urine cotinine was higher among mixed race compared to black African mothers. (Table 2). The sensitivity of self-reported smoking compared to

urine cotinine was much lower for black African (26%) compared to mixed race (85%) participants. However, specificity was high in both groups.

Infant birth outcomes. Only 2 (0.2%) stillbirths occurred. The median gestational age at delivery was 39 (IQR 38 – 40) weeks overall, with 16% (mostly late) preterm births. Median birthweight was significantly higher in black African [3130 (IQR 2800 – 3440) grams] compared to mixed race infants [2980 (IQR 2590-3350) grams]. The median WfA z-score at birth was -0.6 (IQR -1.3 – 0.1) overall, and was substantially lower in mixed race infants. Low birth weight (LBW; <2500g) was observed in 15% of infants, and more than one-quarter were SGA. Only 45 (6%) infants had documented respiratory distress at birth (Table 1). Most (83%) mother-infant pairs were discharged from hospital within 48 hours of delivery.

Infant smoke exposure. Household smokers (including mothers) were reported in almost two-thirds of homes. The prevalence of household smoking was significantly higher in mixed race families where one or more household members reportedly smoked in 83% of homes (Table 2). Excluding maternal smokers, the reported number of other family and household smokers was high at both sites, with 142 (38%) black African and 264 (77%) mixed race participants reporting other smokers.

Urine cotinine measures were obtained in 241 infants at birth and 291 infants at 6-10 weeks. At birth, 56% of infants had urine cotinine indicating exposure with 18% having levels comparable with active smoking, significantly higher in mixed race (33%) compared to black African (4%) infants (Table 2). The prevalence of passive smoke exposure was similar across site.

At 6-10 weeks, half (50%) of infants had cotinine levels indicative of passive smoke exposure, with a much higher prevalence in mixed race (69%) compared to black African (28%) infants. There were few infants (3%) with levels indicative of active smoking (Table 2).

Higher infant urine cotinine levels at birth were associated with maternal smoking (both self-reported and based on cotinine measurements); infants born to mothers classified as active smokers had an almost 15-fold increased risk of testing positive for smoke

exposure. At 6-10 weeks, infant urine cotinine levels were associated with increasing number of household smokers, with infants exposed to 3 or more household smokers having a 4-fold increased risk of testing positive for smoke exposure (Table 3).

Tobacco smoke exposure and birth outcomes. Associations were observed between maternal urine cotinine and a number of adverse birth outcomes in crude analysis. Maternal smoking was significantly associated with a reduction in infant WfA z-score, and with an increased risk of LBW and SGA. (Table 4).

Although associations between maternal urine cotinine and LBW and SGA were no longer significant in adjusted analyses, active smoking remained significantly associated with decreased WfA. Infants born to mothers who were active smokers during pregnancy had, on average, a 0.3 [0.1 - 0.5] z-score decrease in WfA at birth compared to infants born to non-smoking mothers, independent of recruitment site, maternal age, SES, and antenatal alcohol use. In addition, antenatal alcohol use remained an independent predictor of decreased WfA, and was associated with a 0.3 [0.1 – 0.4] z-score decrease in WfA. (Table 5).

Similar results were observed when comparing birth outcomes across categories of infant urine cotinine measured at birth. No associations were observed between infant cotinine and any of gestational age at delivery, pre-term birth, LBW, or respiratory distress at birth. In crude analysis, however, infant cotinine was significantly associated with both a reduction in WfA z-score and an increased likelihood of SGA. Notably, the association between infant cotinine and decreased WfA persisted in adjusted analyses. Infants in the active smoker category had, on average, a 0.6 [0.2 - 1.1] z-score decrease in WfA at birth compared to infants in the non-smoker category, independent of recruitment site, SES, maternal age, and maternal antenatal alcohol use (results not shown).

4 Discussion

This study has shown an alarmingly high prevalence of objectively assessed antenatal and early-life tobacco smoke exposure in infants in this low socioeconomic population. Almost two-thirds of infants had evidence of smoke exposure at birth, while more than 50% were exposed at 6-10 weeks of age. Further the degree of smoke exposure is

concerning, with 18% of infants having birth urine cotinine values in the 'active smoker' range. This prevalence of smoke exposure is much higher than those previously reported globally.[2] Notably, smoke exposure was associated with lower birth weight, a risk factor for respiratory disease and other long-term health effects. [9, 10, 28]

Mothers were a major source of smoke exposure, especially in the mixed race population, with 46% of mixed race women reporting antenatal smoking. This is as much as 10 times the global estimate for pregnant women in LMICs particularly in Africa. [2, 29, 30] Further, the psychosocial stressors affecting participants were considerable with a high prevalence of antenatal depression and recent IPV.

The high prevalence of self-reported smoking was confirmed with maternal urine cotinine testing, with surprisingly high sensitivity of self-report, especially in the mixed race community (85%). The lower sensitivity and lower prevalence of smoking in the black African population may reflect cultural differences in acceptability of cigarette smoking, perhaps contributing to under-reporting. [31]

Although nicotine dependence was low or low-moderate in most mothers, this may be explained by patterns of cigarette use in these impoverished communities, where cost often results in fewer cigarettes smoked. In contrast, scores on the ASSIST indicated that the majority were at moderate to high risk of tobacco-related health problems and could benefit from tobacco cessation programmes. While the most effective smoking cessation programmes rely on a combination of counselling and medication interventions, given the potentially low rates of physical dependency (based on Fagerström test findings), brief behavioural interventions (that include building readiness and motivation to change) may be useful for facilitating reductions in tobacco-related health problems; however, medication-assisted therapy may be necessary in those showing higher rates of dependency.[32, 33]

Household smokers were another major source of on-going smoke exposure, with household smoking again more prevalent in the mixed race (84%) compared to black African community (43%). Increasing number of household smokers was associated with positive urine cotinine measurements in infants, confirming more exposure.

Such intense, early smoke exposure may have profound effects on child health. In this study, smoke exposure was associated with decreased birthweight, a well-described association in both middle and high income countries. [9, 10, 34] Notably, this association persisted even when adjusted for potential confounders. Smoke-exposed children have a higher risk of developing pneumonia, wheezing disorders and chronic respiratory diseases.[6, 7, 15, 35] The cumulative and long-term effects of early and ongoing exposure on child health are currently being longitudinally studied in this cohort.

Several limitations of these findings must be noted, including the fairly small sample size. In addition, although maternal urine cotinine was obtained in all mothers, urine collection was somewhat less successful in infants. As the half-life of cotinine is 17 hours, the prevalence of active smoking or smoke exposure may have been under-estimated if a urine sample was obtained after this time period. These data therefore provide a minimum estimate of smoking and exposure. This analysis was limited to tobacco smoke exposure in the antenatal and early postnatal period; further study of ongoing smoke exposure is underway.

To our knowledge, this is the first study to quantify such exposure at birth, using a combination of maternal and infant measures as well as subjective and objective assessments and highlights the urgent need to develop and implement effective interventions for smoking cessation in pregnant women.[15, 32, 33] In addition, public health interventions and educational initiatives that highlight the risk of household tobacco smoking to adult and child health are urgently needed among vulnerable groups in poor communities.

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AV, WB and HJZ conceptulised the study. KB was responsible for data analysis. RPG, DJS, NK contributed to the study design. AV, WB, NK recruited patients and collected data. AV, BM, RPG and HJZ interpreted data. AV, KB, BM, HJZ drafted the manuscript All authors contributed to the writing of the manuscript and approved the submitted manuscript.

Table 1 Maternal baseline demographic characteristics and infant birth outcomes

Variable	Mbekweni – *n* (%)	TC Newman – *n* (%)	Total – *n* (%)	*P*-value
Maternal baseline demographic characteristics				
Number of mothers	412 (52)	377 (48)	789 (100)	
Median age at enrolment [IQR]	26.7 [22.2, 31.8]	24.8 [21.3, 29.1]	25.7 [21.8, 30.8]	<0.001
Race Black Mixed race	 408 (99) 4 (1)	 5 (1) 372 (99)	 413 (52) 376 (48)	 <0.001
Married/cohabiting	145 (35)	159 (42)	304 (39)	0.044
HIV-infected	154 (37)	11 (3)	165 (21)	<0.001
Educational attainment Primary Some secondary Completed secondary Any tertiary	 41 (10) 219 (53) 124 (30) 28 (7)	 29 (8) 189 (50) 143 (38) 16 (4)	 70 (9) 408 (52) 267 (34) 44 (6)	 0.062
Unemployed	321 (78)	262 (70)	583 (74)	0.007
Average household income <R1000/month R1000-R5000/month >R5000/month	 201 (49) 163 (40) 48 (12)	 130 (34) 176 (47) 71 (19)	 331 (42) 339 (43) 119 (15)	 <0.001
SES quartile Lowest SES Low-moderate SES Moderate-high SES Highest SES	 143 (35) 106 (26) 96 (23) 67 (16)	 70 (19) 90 (24) 97 (26) 120 (32)	 213 (27) 196 (25) 193 (25) 187 (24)	 <0.001
Type of home Informal housing House/flat	 179 (43) 233 (57)	 103 (27) 274 (73)	 282 (36) 507 (64)	 <0.001
Median number of household members (IQR)	4 (3 - 6)	5 (4 - 7)	4 (3 - 6)	<0.001
Antenatal depression – above threshold	87 (21)	76 (20)	163 (21)	0.740
Recent intimate partner violence – above threshold	107 (26)	148 (39)	255 (32)	<0.001
Any self-reported antenatal alcohol use	33 (8)	104 (28)	137 (17)	<0.001

Variable	Mbekweni – *n* (%)	TC Newman – *n* (%)	Total – *n* (%)	*P*-value
Infant birth outcomes				
Number of infants; sets of twins	415 (52); 3	377 (48); 0	792 (100); 3	
Sex – Female	205 (49)	165 (44)	370 (47)	0.113
Median gestation at delivery [IQR]	39 [38, 40]	39 [37, 40]	39 [38, 40]	0.271
Pre-term birth (<37 weeks gestation)	65 (16)	58 (15)	123 (16)	0.914
Median birthweight in grams [IQR]	3130 [2800, 3440]	2980 [2590, 3350]	3080 [2690, 3410]	<0.001
Median WfA z-score [IQR]	-0.4 [-1.2, 0.2]	-0.7 [-1.4, -0.1]	-0.6 [-1.3, 0.1]	<0.001
Low birthweight (LBW; <2500 grams)	48 (12)	74 (20)	122 (15)	0.002
Small for gestational age	96(23)	110(29)	206(26)	0.053
Respiratory distress at birth	23 (6)	20 (5)	43 (5)	0.883

Table 2 Antenatal and early postpartum tobacco smoke exposure

	Mbekweni – *n* (%)	TC Newman – *n* (%)	Total – *n* (%)	*P*-value
Maternal antenatal tobacco smoking, n (%)	412 (52)	377 (48)	789 (100)	
Self-reported current smoking	17 (4)	174 (46)	191 (24)	<0.001
Frequency of smoking (n=191) Daily A few times per week/ month	12 (71) 5 (29)	163 (94) 11 (6)	175 (92) 16 (8)	0.007
Cigarettes smoked daily 10 or less 11-20 21-30 31 or more	16 (94) 1 (6) 0 (0) 0 (0)	163 (94) 5 (3) 2 (1) 2 (1)	179 (94) 6 (3) 2 (1) 2 (1)	0.620
Years smoked – median [IQR; n=191]	4 [2, 6]	6 [4, 10]	6 [4, 10]	0.010

	Mbekweni – *n* (%)	**TC Newman – *n* (%)**	**Total – *n* (%)**	***P*-value**
Pack-years smoked – median [IQR; *n*=191]	0.1 [0.1, 0.3]	1.4 [0.5, 2.7]	1.2 [0.4, 2.5]	<0.001
Nicotine dependence (Fagerström Test; *n*=191) Low Low-moderate Moderate High	 6 (35) 8 (47) 3 (18) 0 (0)	 79 (45) 54 (31) 39 (22) 2 (1)	 85 (45) 62 (32) 42 (22) 2 (1)	0.551
Risk of tobacco-related problems (ASSIST; *n*=183) Lower risk Moderate risk High risk	 0 (0) 10 (83) 2 (17)	 4 (2) 128 (75) 39 (23)	 4 (2) 138 (75) 41 (22)	0.799
Urine cotinine (*n*=789)[1] <10 ng/ml (Non-smoker) 10-499 ng/ml (Passive/ exposed) ≥500 ng/ml (Active smoker)	 134 (33) 221 (54) 57 (14)	 39 (10) 145 (38) 193 (51)	 173 (22) 366 (46) 250 (32)	<0.001
Early postpartum tobacco smoke exposure				
Number of family/household smokers (*n*=720) 0 1 2 3 or more	 215 (57) 124 (33) 31 (8) 6 (2)	 56 (16) 87 (25) 90 (26) 111 (32)	 271 (38) 211 (29) 121 (17) 117 (16)	<0.001
Infant urine cotinine				
Urine cotinine at birth (*n*=241) <10 ng/ml 10-499 ng/ml ≥500 ng/ml	 76 (61) 43 (35) 5 (4)	 30 (26) 48 (41) 39 (33)	 106 (44) 91 (38) 44 (18)	<0.001
Urine cotinine at 6-10 weeks (*n*=291) <10 ng/ml 10-499 ng/ml ≥500 ng/ml	 98 (72) 38 (28) 1 (0.7)	 39 (25) 107 (69) 8 (5)	 137 (47) 145 (50) 9 (3)	<0.001

[1] Antenatal and birth combined, i.e. “Active smoker” if cotinine ≥500 ng/ml for either timepoint

Table 3 Associations between tobacco smoke exposure and infant urine cotinine

Variable	Infant urine cotinine		Risk ratio [95% CI]	*P*-value
	<10 ng/ml – *n* (%)	≥10 ng/ml – *n* (%)		
Associations with infant urine cotinine at birth (n=241)				
Self-reported maternal an-tenatal smoking				
Non-smoker	105 (56)	81 (44)	Reference	
Smoker	1 (2)	54 (98)	2.3 [1.9, 2.7]	<0.001
Maternal antenatal urine cotinine[1]				
Non-smoker (<10 ng/ml)	42 (93)	3 (7)	Reference	
Passive/exposed (10-499 ng/ml)	63 (51)	61 (49)	7.4 [2.4, 22.3]	<0.001
Active smoker (≥500 ng/ml)	1 (1)	71 (99)	14.8 [5.0, 44.2]	<0.001
Associations with infant urine cotinine at 6-10 weeks (n=291)				
Number of family/household smokers				
0	74 (76)	23 (24)	Reference	
1	49 (52)	45 (48)	2.0 [1.3 , 3.1]	<0.001
2	11 (24)	35 (76)	3.2 [2.2, 4.7]	<0.001
3 or more	2 (4)	49 (96)	4.1 [2.8, 5.8]	<0.001

[1] Antenatal and birth combined, i.e. “Active smoker” if cotinine ≥500 ng/ml for either timepoint

Table 4 Unadjusted associations between tobacco smoke exposure and infant birth outcomes

(A) *Association with gestation at delivery*			
Variable	Gestation at delivery – median (IQR)		*P*-value
Maternal antenatal urine cotinine[1]			
Non-smoker (<10 ng/ml)	39 (38 – 40)		0.135
Passive/exposed (10-499 ng/ml)	39 (38 – 40)		
Active smoker (≥500 ng/ml)	39 (37 – 40)		
(B) *Association with pre-term birth*			
Variable	Full term – *n* (%)	Pre-term – *n* (%)	*P*-value
Maternal antenatal urine cotinine[1]			
Non-smoker (<10 ng/ml)	149 (86)	24 (14)	0.715
Passive/exposed (10-499 ng/ml)	312 (85)	57 (15)	
Active smoker (≥500 ng/ml)	208 (83)	42 (17)	
(C) *Association with infant WfA z-score*			
Variable	Infant WfA z-score – median (IQR)		*P*-value
Maternal antenatal urine cotinine[1]			
Non-smoker (<10 ng/ml)	-0.4 (-1.2 – 0.3)		<0.001
Passive/exposed (10-499 ng/ml)	-0.5 (-1.1 – 0.2)		
Active smoker (≥500 ng/ml)	-0.9 (-1.5 – -0.2)		
(D) *Association with infant LBW (<2500g)*			
Variable	≥2500g – *n* (%)	<2500g – *n* (%)	*P*-value
Maternal antenatal urine cotinine[1]			
Non-smoker (<10 ng/ml)	154 (89)	19 (11)	<0.001
Passive/exposed (10-499 ng/ml)	323 (88)	46 (12)	
Active smoker (≥500 ng/ml)	193 (78)	57 (23)	
(E) *Association with infant SGA at birth*			
Variable	AGA/LGA – *n* (%)	SGA – *n* (%)	*P*-value
Maternal antenatal urine cotinine[1]			
Non-smoker (<10 ng/ml)	133 (77)	40 (23)	<0.001
Passive/exposed (10-499 ng/ml)	293 (79)	76 (21)	
Active smoker (≥500 ng/ml)	160 (64)	90 (36)	
(F) *Association with infant respiratory distress at birth*			
Variable	No distress – *n* (%)	Respiratory distress – *n* (%)	*P*-value
Maternal antenatal urine cotinine[1]			
Non-smoker (<10 ng/ml)	163 (94)	10 (6)	0.234
Passive/exposed (10-499 ng/ml)	354 (96)	15 (4)	
Active smoker (≥500 ng/ml)	232 (93)	18 (7)	

[1] Antenatal and birth combined, i.e. “Active smoker” if cotinine ≥500 ng/ml for either timepoint

Table 5 Adjusted associations between tobacco smoke exposure and infant birth outcomes

Variable	(A) Association with WfA z-score		(B) Association with LBW (<2500g)		(C) Association with SGA	
	Unadjusted regression coefficient [95% CI]	**Adjusted regression coefficient [95% CI]**	**Unadjusted risk ratio [95% CI]**	**Adjusted risk ratio [95% CI]**	**Unadjusted risk ratio [95% CI]**	**Adjusted risk ratio [95% CI]**
Maternal urine cotinine[1]						
Non-smoker (<10 ng/ml)	Reference	Reference	Reference	Reference	Reference	Reference
Passive/exposed (10-499 ng/ml)	-0.1 [-0.2, 0.1]	-0.004 [-0.2, 0.2]	1.1 [0.7, 1.9]	1.0 [0.6, 1.6]	1.1 [0.6, 2.0]	0.8 [0.6, 1.2]
Active smoker (≥500 ng/ml)	-0.5 [-0.7, -0.3]	-0.3 [-0.5, -0.1]	2.1 [1.3, 3.4]	1.4 [0.8, 2.4]	2.3 [1.3, 4.1]	1.3 [0.9, 1.9]
Recruitment site						
TC Newman	Reference	Reference	Reference	Reference	Reference	Reference
Mbekweni	0.3 [0.1, 0.4]	0.1 [-0.05, 0.3]	0.6 [0.4, 0.8]	0.6 [0.4, 0.9]	0.8 [0.6, 1.0]	0.9 [0.7, 1.2]
Maternal age at enrolment	0.02 [0.01, 0.03]	0.01 [0.001, 0.03]	1.0 [1.0, 1.02]		1.0 [1.0, 1.0]	
Gravidity						
Multigravida	Reference		Reference		Reference	
Primagravida	-0.4 [-0.5, -0.2]		1.2 [0.9, 1.7]		1.6 [1.3, 2.0]	
SES quartile						
Highest SES	Reference	Reference	Reference	Reference	Reference	Reference
Moderate-high SES	-0.3 [-0.5, -0.1]	-0.3 [-0.5, -0.1]	1.6 [0.9, 2.7]	1.6 [0.9, 2.8]	1.7 [1.2, 2.5]	1.7 [1.1, 2.4]
Low-moderate SES	-0.2 [-0.4, -0.001]	-0.2 [-0.4, 0.02]	1.6 [1.0, 2.8]	1.7 [1.0, 2.9]	1.6 [1.1, 2.3]	1.5 [1.0, 2.2]
Lowest SES	-0.2 [-0.4, -0.02]	-0.2 [-0.4, -0.003]	2.2 [1.3, 3.6]	2.4 [1.4, 4.1]	1.6 [1.1, 2.4]	1.7 [1.1, 2.5]
Maternal HIV infection						
HIV-uninfected	Reference		Reference		Reference	
HIV-infected	0.1 [-0.03, 0.3]		0.8 [0.5, 1.2]		0.9 [0.6, 1.2]	

Variable	(A) Association with WfA z-score		(B) Association with LBW (<2500g)		(C) Association with SGA	
	Unadjusted regression coefficient [95% CI]	**Adjusted regression coefficient [95% CI]**	**Unadjusted risk ratio [95% CI]**	**Adjusted risk ratio [95% CI]**	**Unadjusted risk ratio [95% CI]**	**Adjusted risk ratio [95% CI]**
Antenatal depression						
Below threshold	Reference		Reference		Reference	
Above threshold	-0.2 [-0.4, -0.004]		1.0 [0.7, 1.5]		1.3 [1.0, 1.7]	
Recent intimate partner violence						
Below threshold	Reference		Reference		Reference	
Above threshold	-0.2 [-0.3, -0.0001]		1.5 [1.1, 2.0]		1.2 [1.0, 1.6]	
Antenatal alcohol use						
No alcohol use	Reference	Reference	Reference		Reference	Reference
Any alcohol use	-0.4 [-0.6, -0.2]	-0.3 [-0.4, -0.1]	1.4 [0.9, 2.0]		1.5 [1.1, 1.9]	1.3 [1.0, 1.7]

[1] Antenatal and birth combined, i.e. “Active smoker” if cotinine ≥500 ng/ml for either timepoint

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Indoor air pollution and tobacco smoke exposure: impact on nasopharyngeal bacterial carriage in mothers and infants in an african birth cohort study.

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Take home message:

Indoor air pollution and tobacco smoke exposure impacts on nasopharyngeal bacterial carriage in mothers and infants.

Abstract

Background: Indoor air pollution (IAP) or environmental tobacco smoke (ETS) exposure may influence nasopharyngeal (NP) carriage of bacterial species and development of lower respiratory tract infection (LRTI). Antenatal or postnatal IAP/ETS exposure on NP bacteria in mothers and infants was longitudinally investigated.

Methods: A South African cohort study followed mother-infant pairs from birth through the first year. NP swabs were taken at birth, 6 and 12 months for bacterial culture. Multivariable and multivariate logistic regression investigated associations between NP bacterial species and IAP/ETS. IAP exposures (particulate matter; carbon monoxide; nitrogen dioxide; volatile organic compounds) were measured at home visits. ETS exposure was measured through maternal and infant urine cotinine. Infants received the 13-valent pneumococcal and *Haemophilus influenzae* B conjugate vaccines.

Results: There were 881 maternal and 2605 infant NP swabs. Antenatal ETS exposure was associated with *Streptococcus pneumoniae* carriage in mothers (aOR1.9 (95%CI 1.0-3.5)). Postnatal ETS exposure was associated with carriage in infants (aOR1.5 (95%CI1.0-2.2)). Postnatal carbon monoxide exposure was associated with NP carriage of *Staphylococcus aureus* (aOR2.7 (95%CI 1.0-6.9)), *S. pneumoniae* (aOR2.4 (95%CI 1.1–5.4)) or gram-negative bacilli (aOR4.1 (95% CI 1.0–16.7)) in infants.

Conclusion: Early-life environmental exposures are associated with increased prevalence of specific NP bacteria during infancy, which may predispose to developing LRTI.

1 Background

Nasopharyngeal (NP) microbiota, comprised of a myriad of microorganisms is rapidly acquired after birth and established in infancy.[1, 2] NP carriage of potentially pathogenic bacteria in early life precedes the development of lower respiratory tract infections (LRTI) including pneumonia and bronchiolitis.[3] Understanding the factors that impact on NP carriage may therefore be important in developing strengthened strategies to prevent LRTI, a major cause of death in children in low and middle-income countries (LMIC).

NP carriage may be influenced by several environmental factors including exposure to environmental tobacco smoke (ETS) or indoor air pollution (IAP).[4] Rapid urbanization particularly in LMIC, has resulted in increased use of alternate fuel sources for household energy, with numerous by-products of combustion (including particulate matter, carbon monoxide, nitrogen dioxide and volatile organic compounds) contributing to IAP.[5] Antenatal and early-life exposure to ETS has many potentially detrimental effects on child health including an increased incidence and severity of LRTI.[6, 7]

While studies have assessed the effect of household air pollution on the lung microbiome, [8] no studies have investigated the effects of IAP on NP carriage particularly in infants. However, recently mouse models have shown black carbon (a component of particulate matter) induced structural, compositional and functional changes in bacterial biofilms and their responses to antibiotics as well as facilitated the microaspiration of *Streptococcus spp.* from the nasopharynx to the lung.[9] Further, ETS exposure increases NP carriage of *Streptococcus pneumoniae*[10], alters innate immune mechanisms in the nasal mucosa and disrupts epithelial barriers.[11]

This study longitudinally investigated the impact of antenatal and postnatal IAP and ETS exposure on NP carriage in mothers and infants enrolled in an African birth cohort study, from birth to one year of age.

2 Methods

2.1 Study population and procedures

This study was nested within the Drakenstein Child Health Study (DCHS), a birth cohort in a peri-urban area of South Africa.[12] Consenting pregnant women were enrolled at 20 – 28 weeks' gestation at two public primary health clinics: Mbekweni (serving a predominantly black African population) and Newman (serving a predominantly mixed ancestry population) from March 2012 – July 2015.

All births occurred at a single, central hospital, Paarl hospital. Thereafter, mother-infant pairs were followed at 6, 10 and 14 weeks, 6, 9 and 12 months, for health care and immunisations including the 13-valent pneumococcal conjugate vaccine (PCV-13) given at 6, 14 weeks and 9 months and *Haemophilus influenzae* type b conjugate vaccine at 6, 10, 14 weeks according to the South African Expanded Programme on Immunisation (EPI) schedule.[13] Study questionnaires and clinical data were collected at enrollment and follow-up visits. A validated socio-economic score (SES) was used to categorise participants into quartiles as lowest, low-moderate, moderate-high or highest SES.[5] Clinical data collected at each follow-up visit included details on recent respiratory tract infections, including respiratory symptoms, otitis media, wheeze or LRTI in the preceding month and any antibiotic use in the prior 6 months.

2.2 Assessing environmental exposures

2.2.1 Measuring IAP exposure

The participant's home environment was assessed and dwellings categorized based on having 2 or more defined household dimensions (type of home; building material; water supply; toilet facilities; kitchen type; ventilation in kitchen areas).[5] IAP was measured at home visits conducted antenatally (within 4 weeks of enrollment) and postnatally (between 4-6 months of the infant's life).[5] Home visits were conducted over 3 years with sampling occurring throughout the year covering all seasons and weather conditions. Particulate matter (PM_{10}) and carbon monoxide (CO) were measured by separate monitors (AirChek 52; SKC, Eighty Four, PA, USA for PM_{10} and Altair; Troy, MI, USA for CO)

left in homes over 24 hours. Nitrogen dioxide (NO_2) and volatile organic compounds (VOC), benzene and toluene, were measured using diffusion tubes (Radiello absorbent filters in polyethylene diffusive body; Sigma-Aldrich, St Louis, MO, USA) and (Markes thermal desorption tubes; Llantrisant, UK) left in homes for 2 weeks.[5] These monitors were internally calibrated for temperature and humidity as per manufacturer information and whereas diffusion tubes were corrected for humidity during laboratory analysis.[5, 14] The South African National Ambient Air Quality Standards were used to define expected exposure levels for each pollutant based on an averaging period of 1 year for each measure.[15, 16]

2.2.2 **Measuring ETS exposure**

Maternal, paternal and household tobacco smoking and exposure were assessed using questionnaires administered at enrolment, and antenatal and postnatal visits. These were validated using maternal and infant urine cotinine measures. Maternal cotinine was measured antenatally and at birth, and infant cotinine at birth and 6-10 week with the highest result used to assign smoking status and exposure. Cotinine levels were classified as <10 ng/ml (non-smoker), 10-499 ng/ml, (passive smoker/exposed), or ≥500 ng/ml (active smoker).[7]

2.3 Assessing nasopharyngeal (NP) carriage of bacteria

NP swabs were obtained from mothers (at the time of delivery) and infants at birth, 6 and 12 months by trained study staff according to WHO recommendations[17]. The swabs were immediately stored in 1 ml of skim-milk, tryptone, glucose and glycerol transport medium (STGG), transported on ice to the laboratory and frozen at -80 ^{o}C for later batch processing. After thawing at room temperature (22 ^{o}C), samples were vortexed for 15 seconds before plating out a 10uL aliquot onto four different solid media (National Health Laboratory Services, Green Point Media Laboratory Cape Town, South Africa). Standard laboratory protocols were used for the phenotypic and biochemical identification of common bacterial species that asymptomatically colonise the upper respiratory tract. For *S. pneumoniae* culture, Columbia blood agar base with 2% agar, 5% horse blood and 4 mg/mL gentamicin (CAG) was incubated at 37^{o}C in 5% CO_2 overnight. Presumptive *S.*

pneumoniae isolates were identified by colony morphology, α-hemolysis, optochin disk susceptibility (Oxoid, Basingstoke, UK) and confirmed using *lyt*A PCR.[18] For *H. influenzae,* bacitracin heated blood (BHB) agar plates were incubated at 37°C with 5% carbon dioxide (CO_2). Suspected *H. influenzae* colonies were inoculated onto Columbia agar and identified using Factors X, V and XV discs and by observing growth in the hemolytic zone of *Staphylococcus aureus* on Blood Agar plates. *S. aureus* isolates were identified by culturing on Mannitol Salt Agar (MSA), and DNase testing whereas *Moraxella catarrhalis* isolates were identified by culturing on 2% blood agar, incubated overnight at 37°C. Isolates were presumptively identified by push test and confirmed by *copB* PCR.[19] Gram-negative bacteria were subcultured onto MacConkey agar and identified on Vitek 2® (bioMérieux, Marcy l'Etoile, France).

2.4 Ethics

The study was approved by the Human Research Ethics Committees of the Faculties of Health Sciences, University of Cape Town and Stellenbosch University, and by the Western Cape Provincial Health Research committee (HREC 149/2013). Mothers provided written informed consent at enrolment.

2.5 Statistical analysis

Study data were captured in a relational Microsoft Access® database or collected and managed using REDCap electronic data capture tools hosted at the University of Cape Town .[20] Statistical analyses were conducted in Stata version 14.2 for Windows (Stata Corp, College Station, TX). Statistical tests were considered significant if p value <0.05. Categorical variables were summarised using frequency counts and percentages, n (%). Normally and non-normally distributed continuous variables were described using Mean (SD) and median (IQR) values, respectively. Mann–Whitney or Wilcoxon signed-rank tests, as appropriate, were used to compare medians as well as their spread. Cross tabulations with Fishers' exact or Chi-square tests were used to describe and compare the prevalence of pathogen carriage between the infants (at all time points) and their mothers or between different time points for infants.

Multivariable logistic regression analyses were performed to estimate adjusted odds ratios between each bacterial pathogen and IAP measures (individually or together). The association between antenatal exposures or maternal cotinine and maternal carriage was explored as was the association between postnatal exposures or infant cotinine and infant carriage. The multivariable logistic regressions adjusted for demographic and clinical factors (weight for age z-score at birth, pre-term, ethnicity, sex, HIV exposure, time on exclusive breastfeeding, average number of people per sleeping room, dwelling category, recent respiratory infection, day care attendance, vaccination, number of other children under 5 years in the household, antibiotic use) that have been associated with pathogen acquisition. [21, 22] Further, we explored the possible confounding effects of bacterial co-carriage by including indicator variables for each pathogen.

3 Results

During the study period there were 1137 women enrolled with 1143 live births (4 sets of twins and 1 of triplets), of which 986 infants had at least 1 IAP home measurement and 1 NP swab collected and were included in this analysis. (Fig 1).

3.1 Maternal characteristics

Five hundred and thirty (54%) mothers were enrolled from Mbekweni and 452 /982 (46%) from Newman. The median age of mothers enrolled was 25.8, IQR[22.0, 30.6] years. Significantly more Mbekweni mothers were HIV infected; 193 (36%) compared to Newman, 13 (3%), p <0.001. However, with an effective prevention of mother to child transmission (PMTCT) programme only 2 infants (<1%) were HIV-infected. Unemployment was high in both communities (74%) with more Mbekweni participants in the lowest SES (30%) compared to Newman (18%). (Table 1).

3.2 Infant characteristics

Of the 986 infants included, 484 (49%) were female; the median gestational age was 39 [IQR 38,40] weeks. Most [585 (59%)] infants were not breastfed at 6 months and duration of exclusive breastfeeding was short at 1.4 [IQR 0.7, 3.0] months. Significantly more Newman

infants attended day care at both 6 months (6%) and 12 months(20%) of age compared to Mbekweni infants; 6 month (3%) and 12 months (5%). In 851 (86%) of households there was at least one other child younger than 5-years. Seventy-seven (8%) children reported a recent respiratory infection at 6 months and 51 (5%) at 12 months of age. Antibiotic use was infrequent, (Table 1), while vaccine coverage was high in infants. (Supplemental Table 1)

3.3 Home environment and exposures

Almost 40% of homes were informal and one-third of homes had less than 2 of the defined household dimensions. Electricity access was high (95%), however nearly one-third of Mbekweni homes used alternate fuels for cooking and heating. The median Mbekweni household size was 4 [IQR 3-6] people, smaller than Newman , 5 [IQR 4-7] people. (Table 2)

Of the pollutants measured antenatally, significantly more Mbekweni homes had NO_2 levels above ambient standard compared to Newman [16 (4%) vs. 3(1%)]; overall 45% of homes had measured benzene levels above ambient standards. However, none of the median levels were above ambient standards. For pollutants measured postnatally, there were significant differences across sites in prevalence of above ambient standards for NO_2 (p=0.041) and CO (p= 0.026). (Table 2)

Using maternal cotinine measures, 316 (33%) of mother's were active smokers, significantly higher for Newman, 241 (55%) compared to Mbekweni, 76 (15%) and a further 423 (44%) were exposed to tobacco smoke. For infant ETS exposure, 524 (69%) had cotinine levels indicative of tobacco smoke exposure, of which 104 (14%) were that of a level of active smokers. (Table 2)

3.4 NP bacterial carriage

At delivery, 167/881 (19%; 95%CI 16-22) mothers carried *S. aureus*, 114/881 (13%; 95%CI 11-15) *S.pneumoniae,* 57/881 (6%; 95%CI 5-8) *H.Influenzae*, 59/881 (7%; 95%CI 5-9) *Moraxella catarrhalis* and 18/881 (2%; 95% CI 1-3) other gram-negative bacilli. (Table 3)

At birth, 15/910 (2%; 95%CI 1-4) infants had *S.aureus* while 40/910 (4%; 95%CI 3-6) had gram-negative bacilli on NP samples. By 6 months, 584/887 (66%; 95%CI 63-69) infants carried *S.pneumoniae,* which remained the predominant organism at 1 year of age, carried by 547/800 (68%;95%CI 65-72). However, carriage of *S. aureus* 53/800 (7%; 95%CI 6-9) or gram-negative bacilli 18/800 (2%; 95%CI 1-4) decreased between 6 and 12 months (p<0.001). The median number of bacteria carried was 2 (IQR 1-3) and 2 (IQR 1-2) at 6 and 12 months respectively. (Table 3)

Of the infants who carried *H. influenzae* at 6 months, 160 (50%) continued to carry this at 12 months. Likewise, 376 (74%) of infants who carried *S. pneumoniae* at 6 months also carried *S.pneumoniae* at 12 months, (Supplemental Table 2)

3.5 Associations between environmental exposures and NP carriage

3.5.1 Antenatal exposures and maternal NP carriage

Antenatal exposure to nitrogen dioxide (NO_2) above ambient standards was associated with increased maternal NP carriage of *M. catarrhalis* when adjusted for all clinical co-variates (Adjusted), aOR 4.6 (95% CI 1.4- 15.1) and when adjusted for clinical covariates as well as the other pollutants (Adjusted 2**),** aOR 5.1 (95%CI 1.1 - 23.6).

Benzene exposure was associated with maternal *H. influenzae* carriage when adjusted for clinical covariates (Adjusted); aOR 2.213 95%CI(1.202 - 4.077) and tobacco smoke exposure almost doubled the risk of *S. pneumoniae* carriage in mothers; aOR 1.9 (95% CI 1.0 - 3.4). (Table 4)

3.6 Postnatal exposures and infant NP carriage

ETS exposure was associated with *S. pneumoniae* carriage in infants at 6 months of age [aOR 1.5 (95%CI1.0 - 2.2) (adjusted)] and doubled the risk of carriage of *H. influenzae*; [aOR 2.4 (95%CI 1.1 – 5.6) (adjusted 2)] at 12 months. (Table 5) The association between smoke exposure and *S. pneumoniae* was also noted when adjusting for the other bacterial organisms co-carried (Adjusted); [OR 1.6 (95% CI 1.1 - 2.4)] at 6 months and this association was also seen with gram negative bacilli [aOR 8.5 (95% CI1.0 – 70.9)] at 12 months. (Supplemental Table 3)

Of the IAP measures, only NO_2 was associated with increased gram negative bacilli carriage at 12 months aOR 23.5 (95% CI 1.5 - 364.5). (Table 5) However, when adjusting for co-carriage, clinical covariates and all the other pollutants (Adjusted 2), CO was associated with increased NP carriage of *S. aureus;* OR 2.7 (95%CI 1.0 – 6.9), *S. pneumoniae;* OR 2.4 (95% CI 1.1 – 5.4) or gram negative bacilli; OR 4.1 (95% CI 1.0 – 16.7) in infants at 6 months of age. (Supplemental Table 3)

4 Discussion

In this large peri-urban birth cohort study, we have shown an association between antenatal IAP exposure and maternal NP carriage of bacteria and the impact of tobacco smoke exposure on both maternal and infant bacterial carriage, particularly *S. pneumoniae.* We also report an association between exposure to other indoor air pollutants including carbon monoxide (CO) and nitrogen dioxide(NO_2) on infant bacterial nasopharyngeal carriage.

While it is recognized that several factors including age, season, day care, number of siblings, acute respiratory illness, HIV infection, diet and vaccination may influence the acquisition of NP carriage in infants,[4, 21] the effect of indoor air pollution on NP carriage has not been well described particularly in LMIC.[23] In this study, significant associations between exposure to several indoor air pollutants and maternal and infant NP carriage occurred even after adjusting for such clinical factors associated with carriage and for co-carriage. The associations noted between CO exposure and both *S. aureus and S. pneumoniae* are also significant as the carriage of these microbes are usually inversely correlated.[24] In more detailed studies of the NP flora, *S. aureus* carriage peaks at around 3 months, considerably earlier than *S. pneumoniae* which occurs at around 6 months. As the current study only included infant NP swabs at 6 and 12 months, the relationship between *S. aureus* carriage and *S. pneumoniae* could not be determined. However, given the prevalence *S. aureus* (20% and 7%) and *S. pneumoniae* (66% and 68%) and relatively low co-colonisation with *S. aureus* and *S. pneumoniae* (11% and 4% co-carriage at 6 and 12 months, respectively), it would seem to suggest that there is a negative correlation between *S. aureus* and *S. pneumoniae* colonisation. Nevertheless, postnatal CO

exposure was independently associated with each of these microbes, suggesting that this exposure predisposes to bacterial colonisation with either of these. Although there were no consistent associations between postnatal IAP exposure and infant carriage at both 6 and 12 months, this may reflect both the dynamic nature of bacterial carriage and the complex interplay of a number of factors that influence this and highlights the importance of IAP and ETS exposure in influencing NP bacterial carriage.

In this cohort, maternal smoking and infant in utero and postnatal tobacco exposure was very high as indicated by urine cotinine in both mothers and infants. The high rates of maternal smoking especially amongst mixed race mothers is concerning, as is the very high exposure to household smoke.[7] ETS exposure was associated with increased carriage of several microbes in mothers and infants including *S. pneumoniae, H. influenzae and M. catarrhalis.* NP carriage is recognized as a precursor to LRTI and a source of person-to-person transmission among individuals.[3, 25] Mice models have shown cigarette smoke suppressed nasal inflammatory mediator expression, in particular neutrophil recruiting chemokines normally activated by *S. pneumoniae* carriage, thereby predisposing to invasive *S. pneumoniae* infection. Further, smoking cessation reversed this and prevented invasive pneumococcal disease.[26] Other animal studies have also shown an increased neutrophil response to *H.influenzae* in cigarette exposed mice, with interleukin 1 alpha produced by alveolar macrophages driving this process. This exaggerated response may underlie accelerated lung pathology seen when there is cigarette smoke and bacterial infection.[27] Tobacco smoke also has significant effects on the generation of adaptive immune responses to *H. influenzae* which may predispose to recurrent infections and exacerbations particularly in chronic lung diseases.[28] The host's ability to control bacterial colonisation of the upper airway is also impacted by cigarette smoke with increased inflammatory mediators and reduced blood granulocyte and monocyte phagocytosis activity.[29] These mechanisms may therefore increase the risk of developing LRTI and warrant further investigation.

The association between *S. pneumoniae* NP carriage and the development of subsequent *S. pneumoniae* disease including lower respiratory tract infection (LRTI) is well recognized.[3, 25, 30] Increased *S.pneumoniae* carriage in infants associated with both car-

bon monoxide and ETS exposure suggests that reducing exposure to these pollutants could play a role in the prevention of childhood LRTI. Further, tobacco smoke exposure also doubled maternal NP pneumococcal carriage, providing a source for increased transmission between individuals. While we found no association between preceding respiratory tract infection (either upper or lower respiratory tract infection), on nasopharyngeal bacterial carriage, the association between NP pneumococcal carriage and the development of LRTI (as an outcome) was not explored, as for this study infant NP carriage was assessed at two time points (6 and 12 months) and the majority of LRTI cases occurred early, before 6 months.[31] Similarly, we were unable to assess the effect of pneumococcal conjugate vaccine (PCV) (administered at 6, 14 weeks and 9 months) on *S.pneumoniae* carriage due to the very high vaccination rates and the infrequent sampling period in this study. We have however, previously described the association between IAP and ETS exposure and LRTI in this cohort,[31] highlighting the role of IAP and ETS as potential risk factors for childhood respiratory illness.

The patterns of infant carriage seen in this cohort are consistent with those previously described, with *S. aureus* predominating in the first months, followed by *S. pneumoniae* which persisted till 12 months of age[21, 32]. The predominant maternal bacteria carried was *S. aureus,* however the prevalence is lower than other studies which have reported maternal *S. aureus* carriage of up to 50%.[33-35] The high rates of infant *S. pneumoniae* carriage are also consistent with those reported in low and low-middle income settings[30, 36]. The study extends this knowledge by identifying factors associated with acquisition which have not previously been described in infants. A limitation of this study is reliance on bacterial culture to identify organisms, which may underestimate bacterial prevalence and the inability to sub-type organisms. However, the four most common bacterial species identified are the major contributors to bacterial LRTI in infants. In addition to these species, we also identified a range of gram-negative enteric bacterial species in the nasopharynx, but at a considerably lower frequency, and with insufficient statistical power to draw conclusions. Although standard bacterial culture is likely to miss key components of the bacterial microbiota of the nasopharynx, one of the major advantages of culture over 16S- amplicon sequencing based microbiome studies, is the ability to identify bacteria at the species level.[37] This is highly relevant for nasopharyngeal bacteria, where there is

substantial difference in potential for pathogenicity within a genus. Further, a range of viral infections are likely to impact carriage of bacteria in the nasopharynx, [38] with viral infections playing a mediator role. IAP or ETS exposure may also impact on viral infections,[39] which in turn may influence bacterial carriage. However, a limitation of this study is that comprehensive assessment of viral infections at a range of time points, including time points preceding our analysis of bacterial carriage was beyond the scope of this analysis. Further, we considered multiple hypothesis at once through multiple statistical tests with the consequence that some of the significant associations might be due to chance. Strengths of this study were the large sample size, longitudinal measurements of NP carriage, direct measurements of indoor air pollutants both antenatally and postnatally, testing of maternal and infant samples and comprehensive analysis which considered numerous co-variates.

The association between both IAP and ETS exposure on maternal and infant nasopharyngeal bacterial carriage has not been well described, particularly in LMIC, peri-urban communities who may rely on alternate fuel sources . This study highlights the need for effective, preventative measures to reduce such exposures. The population in this study represent a particularly vulnerable group of poor pregnant women and children in a low and middle-income country setting, where there is a high burden of respiratory disease. Effective strategies to reduce smoking in pregnant women and to minimize household IAP exposure are needed to improve child and maternal health particularly in LMICs.

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Figure 1: Cohort description and samples collected

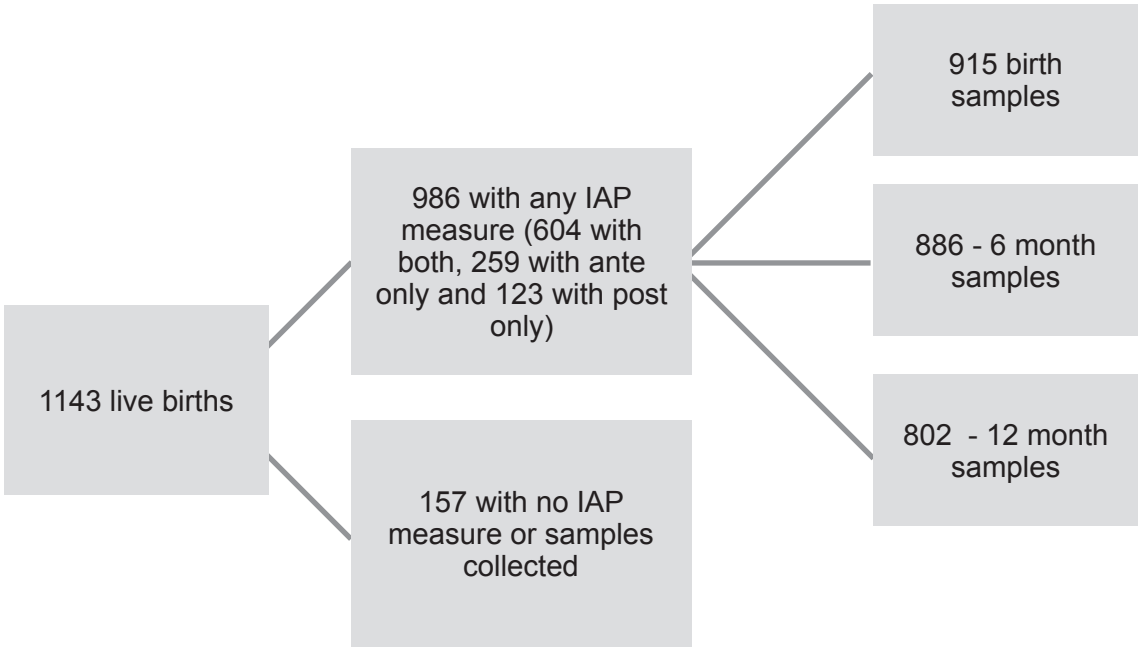

Table 1: Maternal and infant characteristics

	Mbekweni, n (%)	Newman, n (%)	Total, n (%)	*P*-value
Maternal characteristics				
Number of mothers	530 (54)	452 (46)	982 (100)	
Ethnicity Black Mixed ancestry	 523 (99) 7 (1)	 4 (1) 448 (99)	 527 (54) 455 (46)	<0.001
Median age at enrolment [IQR]	26.9 [22.3, 31.6]	24.6 [21.3, 29.1]	25.8 [22.0, 30.6]	<0.001
HIV-infected	193 (36)	13 (3)	206 (21)	<0.001
Unemployed	400 (75)	325 (72)	724 (74)	0.205
SES quartile Lowest SES Low-moderate SES Moderate-high SES Highest SES	 157 (30) 150 (28) 126 (24) 97 (18)	 80 (18) 109 (24) 127 (28) 136 (30)	 237 (24) 259 (26) 253 (26) 233 (24)	<0.001
Median number of household members (IQR)	4 (3 - 6)	5 (4 - 7)	4 (3 - 6)	<0.001

	Mbekweni, n (%)	Newman, n (%)	Total, n (%)	*P*-value
Married / cohabiting	188 (35)	194 (43)	382 (39)	0.017
Infant characteristics and birth outcomes				
Number of infants; sets of twins	534 (54); 4	452 (46); 0	986 (100); 4	
Female	280 (52)	204 (45)	484 (49)	0.022
Median gestation at delivery [IQR]	39 [38, 40]	39 [37, 40]	39 [38, 40]	0.032
Median birthweight in grams [IQR]	3180 [2810, 3460]	2990 [2630, 3340]	3080 [2720, 3415]	<0.001
Median weight-for-age z-score [IQR]	-0.4 [-1.3, 0.2]	-0.7 [-1.4, -0.1]	-0.6 [-1.3, 0.0]	<0.001
Low birthweight (<2500 grams)	55 (10)	83 (18)	138 (14)	<0.001
Pre-term birth (<37 weeks gestation)	16 (3)	19 (4)	35 (4)	0.314
Feeding at 6 months Exclusive breastfeeding Mixed Not breastfeeding	 76 (14) 89 (17) 369 (69)	 66 (15) 170 (38) 216 (48)	 142 (14) 259 (26) 585 (59)	 <0.001
Duration of exclusive breastfeeding, months [IQR]	1.1 [0.5, 3]	1.6 [0.9, 3.0]	1.4 [0.7, 3.0]	0.410
Day care attendance 6 months of age 12 months of age	 17 (3) 69 (13)	 28 (6) 90 (20)	 45 (5) 159 (16)	 0.024 0.003
Additional child under 5 years in household	455 (85)	396 (88)	851 (86)	0.274
Respiratory infection in prior month 6 months of age 12 months of age	 40 (7) 29 (5)	 37 (8) 22 (5)	 77 (8) 51 (5)	 0.685 0.691
Antibiotic use (prior 6 months) 6 months of age 12 months of age	 25 (5) 14 (3)	 38 (8) 13 (3)	 63 (6) 27 (3)	 0.057 0.957

Table 2: Home environment and exposures

	Mbekweni, n (%)	Newman, n (%)	Total, n (%)	*P*-value
Home environment				
Household dimensions [§]				
Has ≤2 dimensions	185 (38)	121 (27)	306 (33)	<0.001
Has > 2 dimensions	302 (62)	320 (73)	622 (67)	
Alternate fuel used (coal, wood, paraffin, gas)				
Cooking	133 (31)	37 (10)	170 (21)	<0.001
Heating	127 (29)	7 (2)	134 (16)	<0.001
Crowding (median, IQR)				
Household size	4 (3-6)	5 (4-7)	4 (3-6)	<0.001
Persons per sleeping room	3 (2-4)	3 (2-5)	3 (2-5)	0.010
Pollutants measured – antenatal				
Particulate matter (PM_{10}) g/m^3	32.0	35.6	33.4	0.417
(n= 755)	[12.3, 64.2]	[12.8, 65.6]	[12.4, 65.6]	0.853
Above threshold	73 (19)	65 (18)	138 (18)	
Nitrogen dioxide (NO_2) µg/m^3				
(n= 747)	7.3 [2.6, 14.6]	7.1 [3.9, 11.3]	7.1 [3.4, 12.7]	0.494
Above threshold	16 (4)	3 (1)	19 (3)	0.005
Benzene µg/m^3 (n= 729)	4.6 [1.5, 17.9]	3.9 [1.8, 8.6]	4.3 [1.8, 11.0]	0.475
Above threshold	183 (47)	147 (43)	330 (45)	0.244
Toluene µg/m^3 (n= 729)	16.1 [5.9, 43.0]	17.4 [8.2, 46.5]	16.9 [7.2, 44.6]	0.282
Above threshold	36 (9)	30 (9)	66 (9)	0.803
Carbon monoxide (CO) mg/m^3				
(n= 706)	0.0 [0.0, 5.1]	0.0 [0.0, 8.4]	0.0 [0.0, 7.6]	0.144
Above threshold	39 (10)	42 (14)	81 (11)	0.095
Pollutants measured - postnatal				
Particulate matter (PM_{10}) g/m^3	30.0 [14.7, 49.7]	28.4	29.3	0.364
(n= 505)		[10.5, 53.7]	[12.6, 52.5]	0.499
Above threshold	38 (16)	36 (14)	74 (15)	
Nitrogen dioxide (NO_2) µg/m^3				
(n= 532)	6.3 [2.9, 14.6]	5.3 [2.6, 11.3]	5.8 [2.6, 12.67]	0.119
Above threshold	6 (2)	1 (0)	7 (1)	0.041
Benzene µg/m^3 (n= 462)	2.8 [0.8, 14.4]	3.2 [1.5, 7.6]	3.1 [1.1, 9.5]	0.345
Above threshold	95 (39)	75 (35)	170 (37)	0.426

	Mbekweni, n (%)	Newman, n (%)	Total, n (%)	*P*-value
Toluene µg/m^3 (n= 462) Above threshold	15.1 [4.9, 50.0] 24 (10)	15.9 [6.5, 51.7] 23 (11)	15.5 [5.9, 50.0] 47 (10)	0.342 0.728
Carbon monoxide (CO) mg/m^3 (n= 502) Above threshold	 0.0 [0.0, 0] 17 (7)	 0.0 [0.0,5.6] 30 (12)	 0.0 [0.0, 0] 47 (9)	 0.018 0.026
Maternal antenatal tobacco smoking, n (%)				
Number of mothers	530	451	981	
Maternal Urine cotinine (*n*=954)	512	442		
<10 ng/ml (Non-smoker)	181 (35)	47 (11)	228 (24)	<0.001
10-499 ng/ml (Passive/exposed)	255 (50)	155 (35)	410 (43)	
≥500 ng/ml (Active smoker)	76 (15)	240 (54)	316 (33)	
Infant urine cotinine				
Urine cotinine at birth or 6-10 weeks (n=763)	415	348		
<10 ng/ml	184 (44)	55 (16)	239 (31)	<0.001
10-499 ng/ml	212 (51)	208 (60)	420 (55)	
≥500 ng/ml	19 (5)	85 (24)	104 (14)	

§ Dimensions comprise: type of home; building material; water supply; toilet facilities; kitchen type; ventilation in kitchen areas

Table 3: Nasopharyngeal bacterial carriage at birth, 6 months and 1 year of life

	Maternal	Infants		
	At time of birth, n (%) (95% CI) n= 881	**At birth, n (%) (95%CI) n= 911**	**At 6 months, n (%) (95%CI) n= 887**	**At 1 year, n (%) (95%CI) n= 800**
S. aureus	167 (19)(16-22)	15 (2)(1-4)	172 (19)(17-22)	53 (7)(6-9)
S. pneumoniae	114 (13)(11-15)	2 (0)(0-1)	584 (66)(63-69)	547 (68)(65-72)
H. influenzae	57 (6)(5-8)	2 (0)(0-1)	371 (42)(39-45)	335 (42)(38-45)
M. catarrhalis	59 (7)(5-9)	8 (1)(0-2)	452 (51)(48-54)	435 (54)(51-58)
Gram negative bacilli	18 (2)(1-3)	39 (4)(3-6)	63 (7)(6-9)	18 (2)(1-4)
Median number of bacterial species [IQR]	0 [0-1]	0 [0-0]	2 [1-3]	2 [1-2]

Table 4: Multivariate analysis of antenatal exposures and maternal nasopharyngeal bacterial carriage.

	S. aureus		***S. pneumoniae***		***H. influenzae***		***M . catarrhalis***		**Gram negative bacilli**	
	Adjusted OR (CI)	Adjusted 2 OR (CI)	Adjusted OR (CI)	Adjusted 2 OR (CI)	Adjusted OR (CI)	Adjusted 2 OR (CI)	Adjusted OR (CI)	Adjusted 2 OR (CI)	Adjusted OR (CI)	Adjusted 2 OR (CI)
PM_{10}	0.96 (0.58 -1.6)	1.2 (0.70 - 2.27)	0.84 (0.45 - 1.5)	0.60 (0.27 - 1.3)	0.89 (0.40 – 2.0)	1.0 (0.44 - 2.4)	0.67 (0.25 - 1.7)	0.47 (0.13 - 1.7)	0.88 (0.19 - 4.1)	1.2 (0.23 – 6.0)
NO_2	1.1 (0.35 - 3.5)	1.8 (0.45 – 7.9)	0.93 (0.21 - 4.2)	1.7 (0.34 – 9.2)	2.0 (0.44 - 9.6)	1.3 (0.14 – 11.4)	4.6 (1.4 – 15.1)	5.1 (1.1 – 23.6)	-	-
Benzene	0.65 (0.43 - 0.97)	0.60 (0.35 - 1.0)	1.0 (0.65 - 1.6)	1.1 (0.56 – 2.0)	2.2 (1.2 - 4.1)	1.7 (0.81 – 3.7)	1.5 (0.82 - 2.8)	2.3 (0.88 - 6.1)	2.5 (0.75 - 8.5)	1.3 (0.28 - 6.5)
CO	0.80 (0.51 - 1.3)	0.68 (0.40 - 1.2)	1.1 (0.63 - 1.8)	1.0 (0.54 - 1.9)	1.4 (0.70 - 2.7)	1.1 (0.52 - 2.3)	0.61 (0.28 - 1.3)	0.73 (0.27 - 1.9)	0.63 (0.17 - 2.3)	0.53 (0.10 - 2.8)
Smoking	0.98 (0.64 - 1.5)	0.92 (0.53 - 1.6)	1.9 (1.0 - 3.4)	1.6 (0.76 - 3.4)	0.81 (0.41 - 1.6)	1.0 (0.42 - 2.6)	1.1 (0.54 - 2.1)	0.90 (0.34 - 2.2)	0.83 (0.27 - 2.5)	1.5 (0.29 - 8.0)
Toluene	0.55 (0.24 - 1.3)	0.67 (0.26 - 1.8)	1.6 (0.81 - 3.3)	2.1 (0.87 - 4.8)	1.1 (0.43 - 3.1)	1.1 (0.37 - 3.2)	1.8 (0.72 - 4.5)	1.7 (0.51 - 5.3)	3.6 (0.95 - 14.0)	3.5 (0.65 - 18.7)

Notes:

Odds ratios in bold are statistically significant at $p<0.05$

Adjusted for all the clinical-demographic variables

Adjusted 2 for all the clinical-demographic variables, plus adjusting for other indoor air pollutants

PM_{10} = particulate matter, NO_2 = nitrogen dioxide, CO = carbon monoxide

Table 5: Multivariate analysis of postnatal exposures and infant nasopharyngeal bacterial carriage

Adj. OR (CI)		*S. aureus*		*S. pneumoniae*		*H. influenzae*		*M. catarrhalis*		Gram negative bacilli	
		Adj. 2 OR (CI)	Adj. OR (CI)	Adj. 2 OR (CI)	Adj. OR (CI)	Adj. 2 OR (CI)	Adj. OR (CI)	Adj. 2 OR (CI)	Adj. OR (CI)	Adj. 2 OR (CI)	
PM_{10}	6 mth	0.97 (0.49 - 1.9)	0.91 (0.33 - 2.5)	0.89 (0.53 - 1.5)	0.94 (0.43 – 2.0)	1.2 (0.71 – 2.0)	2.1 (0.92– 4.7)	0.82 (0.48 - 1.4)	0.77 (0.36 - 1.7)	0.58 (0.17 - 2.0)	0.12 (0.014 – 1.1)
	12 mth	0.55 (0.12 - 2.4)	1.7 (0.29 – 9.5)	1.1 (0.58 – 2.0)	0.87 (0.35 – 2.1)	1.3 (0.77 – 2.3)	1.1 (0.44 - 2.6)	1.3 (0.73 - 2.2)	2.3 (0.97 – 5.6)	0.91 (0.11 - 7.9)	4.0 (0.085 - 188.8)
NO_2	6 mth	0.92 (0.10 - 8.3)	-	3.1 (0.36 – 27.0)	-	0.37 (0.068 - 2.0)	-	0.91 (0.18 - 4.7)	-	3.5 (0.36 – 34.5)	-
	12 mth	-	-	1.5 (0.16 - 13.4)	-	0.52 (0.088 - 3.1)	-	0.32 (0.055 - 2.9)	-	23.5 (1.5 - 364.5)	-
Benzene	6 mth	0.73 (0.43 - 1.23)	0.72 (0.28 - 1.9)	1.0 (0.67 - 1.5)	0.60 (0.28 - 1.3)	0.92 (0.62 - 1.4)	0.96 (0.43 - 2.1)	0.93 (0.63 – 1.4)	0.95 (0.48 - 1.9)	0.62 (0.25 - 1.6)	0.33 (0.079 – 1.4)
	12 mth	0.80 (0.33 – 1.9)	0.85 (0.13 – 5.7)	1.1 (0.67 – 1.7)	1.7 (0.70 – 4.3)	0.69 (0.5 – 1.1)	0.79 (0.35 - 1.8)	0.79 (0.52 – 1.2)	0.81 (0.37 - 1.8)	2.1 (0.48– 9.5)	2.6 (0.13 - 53.2)
CO	6 mth	1.3 (0.75 - 2.3)	1.9 (0.81 - 4.4)	1.1 (0.70 - 1.8)	2.0 (1.0 -4.321)	1.1 (0.69 - 1.7)	0.90 (0.41 - 1.9)	1.1 (0.68 – 1.8)	1.5 (0.74 – 3.2)	1.2 (0.44 - 3.1)	2.7 (0.80 - 9.4)
	12 mth	0.66 (0.21- 2.1)	0.74 (0.12 – 4.6)	1.2 (0.71 - 2.0)	1.5 (0.63 – 3.4)	1.0 (0.62 - 1.7)	1.0 (0.47 - 2.3)	1.0 (0.61 - 1.6)	1.0 (0.50 - 2.2)	1.6 (0.37 - 7.3)	1.9 (0.1 – 31.1)

Adj. OR (CI)		*S. aureus*		*S. pneumoniae*		*H. influenzae*		*M. catarrhalis*		Gram negative bacilli	
		Adj. 2 OR (CI)	**Adj. OR (CI)**	**Adj. 2 OR (CI)**	**Adj. OR (CI)**	**Adj. 2 OR (CI)**	**Adj. OR (CI)**	**Adj. 2 OR (CI)**	**Adj. OR (CI)**	**Adj. 2 OR (CI)**	
Smoking	6 mth	1.4 (0.85 – 2.2)	0.77 (0.34-1.8)	1.5 (1.0 - 2.2)	1.4 (0.72 - 2.9)	0.89 (0.61 - 1.3)	0.81 (0.39 - 1.7)	0.98 (0.68 - 1.4)	1.2 (0.61 - 3.4)	0.88 (0.42 – 1.8)	0.63 (0.19 – 2.1)
	12 mth	0.76 (0.37 - 1.6)	0.86 (0.16 – 4.5)	1.0 (0.66- 1.5)	0.79 (0.33 - 1.9)	1.4 (0.93 – 2.1)	2.4 (1.1 – 5.6)	1.1 (0.71 – 1.6)	1.2 (0.56 – 2.6)	7.2 (0.89 – 59.0)-	-
Toluene	6 mth	0.51 (0.21 - 1.3)	0.80 (0.19 – 3.5)	0.87 (0.46 - 1.7)	1.5 (0.50 – 4.7)	0.79 (0.42 - 1.5)	0.39 (0.11 - 1.4)	0.88 (0.47 - 1.6)	-	-	-
	12 mth	0.81 (0.18 - 3.6)	-	1.4 (0.63 – 3.0)	0.97 (0.25 – 3.7)	1.3 (0.66 - 2.6)	-	1.4 (0.72 - 2.8)	0.77 (0.24 – 2.5)	-	-

Notes:

1. Odds ratios in bold are statistically significant at $p<0.05$
2. Adjusted for all the clinical-demographic variables.
3. Adjusted 2 for all the clinical-demographic variables, plus adjusting for other indoor air pollutants
4. PM_{10} = particulate matter, NO_2 = nitrogen dioxide, CO = carbon monoxide

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Supplemental information

Supplemental Table 1: Vaccine coverage, as per the South African expanded programme on immunisation schedule

Samples		**Vaccines, n (%)**							
Time of collection	Number of results	Bacillus Calmette-Guérin (BCG)	Diptheria / tetanus / pertussis (DTP)			Measles	Pneumococcal conjugate vaccine, 13-valent (PCV)		
		Birth	6 Weeks	10 Weeks	14 Weeks	9 Months	6 weeks	14 Weeks	9 Months
Birth	911	828 / 830 (99.8%)	-	-	-	-	-	-	-
6 Months	887	831 / 834 (99.6%)	839 / 840 (99.9%)	834 / 834 (100%)	823 / 826 (99.6%)	-	840 / 840 (100%)	824 / 826 (99.8%)	-
12 Months	800	751 / 752 (99.9%)	761 / 762 (99.9%)	758 / 759 (99.9%)	747 / 751 (99.5%)	706 / 713 (99.0%)	762 / 762 (100%)	749 / 752 (99.6%)	709 / 718 (98.8%)

Supplemental Table 2: Carriage status of infants at 12 months, relative to infant carriage at 6 months of age

Negative, n (%)		6 Months		
		Positive, n (%)	*P*-value	
12 Months	*S. aureus*	39 (6)	12 (8)	0.454
	S. pneumoniae	154 (57)	376 (74)	<0.001
	H. influenzae	165 (36)	160 (50)	<0.001
	M. catarrhalis	197 (51)	227 (57)	0.084
	Gram negative bacilli	15 (2)	2 (4)	0.444

Supplemental Table 3: Multivariate analysis of postnatal exposures and infant nasopharyngeal bacterial carriage adjusting for bacterial co-carriage.

Adjusted OR (CI)		*S. aureus*		*S. pneumoniae*		*H. influenzae*		*M. catarrhalis*		Gram negative bacilli	
		Adj. 2 OR (CI)	Adjusted OR (CI)	Adj. 2 OR (CI).	Adjusted OR (CI)	Adj. 2 OR (CI)	Adjusted OR (CI)	Adj. 2 OR (CI)	Adjusted OR (CI)	Adj. 2 OR (CI)	Adjusted OR (CI)
PM^{10}	6 months	0.82 (0.41 – 1.6)	1.1 (0.36 - 2.)	0.84 (0.49 - 1.)	0.73 (0.32 - 1.7)	1.4 (0.67 – 2.0)	1.2(0.50 – 3.0)	0.94 (0.56 - 1.6)	0.66 (0.29 – 1.5)	0.66(0.22 - 2.0)	0.093 (0.010 – 0.85)
	12 months	0.54 (0.11 – 2.4)	1.6 (0.27 – 9.6)	1.0 (0.58 - 1.9)	0.90 (0.38 – 2.1)	1.4 (0.78 - 2.3)	1.2 (0.50 - 3.0)	1.1 (0.64 - 1.9)	1.9 (0.80 – 4.5)	0.90 (0.098 - 8.2)	-
NO_2	6 months	0.71 (0.079 – 6.4)	-	3.6 (0.41 - 31.0)	-	0.36(0.064 - 2.0)	-	1.3 (0.28 - 6.3)	-	2.4 (0.4 - 23.)	-
	12 months	-	-	1.90 (0.21- 17.3)	-	0.59 (0.094 – 3.7)	-	0.40(0.068 - 24)	-	16.3 (0.84 - 316.6)	-
Benzene	6 months	0.68 (0.40 - 1.1)	0.60 (0.23 - 1.6)	1.0 (0.66 - 1.5)	0.61 (0.29 - 1.3)	0.89 (0.59 - 1.3)		0.90 (0.60 - 1.3)	0.92(0.45 - 1.9)	0.72 (0.31 - 1.7)	0.21 (0.045 - 0.95)
	12 months	0.76 (0.31 - 1.9)	0.52 (0.078 - 3.4)	1.1 (0.69 - 1.7)	1.6 (0.69 – 3.6)	0.72 (0.47 - 1.1)	0.91 (0.40 – 2.0)	0.83(0.54 - 1.3)	0.73 (0.34 - 1.6)	1.9 (0.41 – 8.3)	-
CO	6 months	1.40 (0.90 - 2.5)	2.7 (1.0 - 6.9)	1.1 (0.67 - 1.8)	2.4 (1.1 – 5.4)	1.1 (0.67 - 1.7)	1.0 (0.44 – 2.3)	1.1 (0.70 - 1.7)	1.4 (0.66 – 3.0)	1.0 (0.38 - 2.7)	4.1 (1.0 – 16.7)
	12 months	0.72 (0.23 - 2.2)	0.80 (0.13– 5.1)	1.2 (0.71 - 2.0)	1.7 (0.73 – 3.8)	0.97(0.59 - 1.6)	1.0 (0.44 - 2.3)	1.0 (0.62 - 1.6)	1.2 (0.53 – 2.6)	1.62(0.35 - 7.5)	-
Smoking	6 months	1.4 (0.86 - 2.3)	0.81 (0.33 - 2.0)	1.6 (1.1 - 2.4)	1.5 (0.72 - 3.2)	0.85 (0.58 - 1.3)	2.2 (0.93- 5.0)	1.0 (0.69- 1.47)	1.0 (0.51 – 2.1)	0.99 (0.47 - 2.1)	0.87 (0.26 – 2.9)
	12 months	0.75 (0.36 - 1.6)	0.70 (0.13 – 3.8)	1.0 (0.66 – 1.5)	0.97 (0.42 – 2.2)	1.3 (0.87 - 2.0)	2.2 (0.93 – 5.0)	1.1 (0.73 – 1.6)	1.3 (0.57 – 2.8)	8.6 (1.0 – 70.9)	-

Adjusted OR (CI)		*S. aureus*		*S. pneumoniae*		*H. influenzae*		*M. catarrhalis*		Gram negative bacilli	
		Adj. 2 OR (CI)	**Adjusted OR (CI)**	**Adj. 2 OR (CI).**	**Adjusted OR (CI)**	**Adj. 2 OR (CI)**	**Adjusted OR (CI)**	**Adj. 2 OR (CI)**	**Adjusted OR (CI)**	**Adj. 2 OR (CI)**	**Adjusted OR (CI)**
Toluene	6 months	0.51 (0.20 - 1.3)	-	0.83 (0.43 - 1.6)	-	0.73 (0.38 - 1.4)	-	0.81 (0.43 - 1.5)	-	0.28 (0.036 - 2.2)	-
	12 months	0.86 (0.19 - 3.9)	-	1.2 (0.57 – 2.6)-	-	1.1 (0.56 - 2.2)	-	1.4 (0.69 - 2.8)	-	-	-

Notes:

1. Odds ratios in bold are statistically significant at $p<0.05$
2. Adjusted for co-carriage – the presence or absence of the other organisms, plus all the clinical-demographic variables
3. Adjusted 2 for co-carriage – the presence or absence of the other organism, plus all the clinical-demographic variables, plus adjusting for other indoor air pollutants.
4. PM_{10} = particulate matter, NO_2 = nitrogen dioxide, CO = carbon monoxide

Early-life exposure to indoor air pollution or tobacco smoke and lower respiratory tract illness and wheezing in African infants: a longitudinal birth cohort study.

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Running Head: Environmental exposures and respiratory disease in African infants

Descriptor: 1·17 Epidemiology (Paediatrics): risk factors

Research in context

Evidence before this study

Environmental exposures from indoor air pollution (IAP) or environmental tobacco smoke are important risk factors for childhood lower respiratory tract illness (LRTI) or wheezing, but there are few data on the impact of antenatal compared to postnatal exposures and from low or middle income country (LMIC) and African settings, which have a high burden of illness. Further there is a paucity of data on the impact of exposure to new alternate sources of fuel, including volatile organic compounds (VOCs), increasingly used globally. We searched PubMed, Scopus and Google Advanced Scholar using the search terms “child”, “ indoor air pollution (IAP)”, “tobacco smoke”, “pneumonia”, “respiratory tract infection”, “wheezing” for English articles from 1990 – 2017. We focused on studies particularly from LMICs that studied the effects of environmental exposures (either IAP or tobacco smoke) with paediatric respiratory health as an outcome. These studies reported an association between environmental exposures and childhood LRTI or wheezing with IAP associated with an almost double risk of developing LRTI in a systematic review. A similar increase was reported in a systematic review of ETS exposure and LRTI or wheezing, which found that both parental and household smokers significantly increased the risk of LRTI. However, the strongest effect was on bronchiolitis with household smokers more than doubling this risk.

Highlighting a critical gap, we found little data differentiating timing of exposures i.e. antenatal vs postnatal and no longitudinal African data. Further, most studies relied on reported environmental exposures or modelled data, rather than direct measurement of exposures and none measured new exposures like VOCs.

Added value of this study

In this African birth cohort study, in which exposures were objectively and longitudinally measured antenatally and postnatally, LRTI or wheezing was common and associated with antenatal rather than postnatal exposure to ETS or to IAP. Antenatal exposure to toluene, a VOC, was identified as a novel exposure associated with LRTI, hospitalisation

and severe disease. Both antenatal and postnatal maternal smoking were associated with wheezing. This study provides novel data on new exposures such as VOCs which are increasingly used as alternate fuel sources globally. Further the study highlights the importance of exposures in the antenatal rather than the postnatal period in determining child respiratory health.

Implications of all the available evidence

Preventive strategies should focus on women of child bearing age in the prenatal period to reduce ETS and IAP exposure. Alternate sources of fuel may not be as safe as currently regarded; further study of these is needed. Effective public health interventions targeting environmental antenatal and early-life exposures are needed to promote child respiratory health.

Summary

Background Indoor air pollution (IAP) and environmental tobacco smoke (ETS) are associated with lower respiratory tract illness (LRTI) or wheezing in children. However, the effect of the timing of these exposures, specifically antenatal versus postnatal, and of alternate fuel sources such as the increasingly used volatile organic compounds have not been well studied. We longitudinally investigated the effect of antenatal or postnatal IAP and ETS on LRTI or wheezing prevalence and severity in African infants.

Methods Mother and infant pairs enrolled over a 3-year period in a birth cohort study in two centres in Paarl, South Africa, were followed for the first year of life for LRTI or wheezing illness. We measured exposure to IAP (particulate matter, nitrogen dioxide, sulphur dioxide, carbon monoxide, and volatile organic compounds benzene and toluene) using devices placed in homes, antenatally and postnatally. We measured ETS longitudinally by maternal self-report and by urine cotinine measures. Study staff trained in recognition of LRTI or wheeze documented all episodes, which were categorised according to WHO case definition criteria. We used multivariate logistic and Poisson regressions to explore associations.

Findings Between March 1, 2012, and March 31, 2015, we enrolled 1137 mothers with 1143 livebirths. Of 1065 infants who attended at least one study visit, 524 episodes of LRTI occurred after discharge with a wheezing prevalence of 0·23 (95% CI 0·21–0·26) episodes per child year. Exposures associated with LRTI were antenatal maternal smoking (incidence rate ratio 1·62, 95% CI 1·14–2·30; p=0·004) or particulate matter (1·43, 1·06–1·95; p=0·008). Subanalyses of LRTI requiring hospitalisation (n=137) and supplemental oxygen (n=69) found antenatal toluene significantly increased the risk of LRTI-associated hospitalisation (odds ratio 5·13, 95% CI 1·43–18·36; p=0·012) and need for supplemental oxygen (13·21, 1·96–89·16; p=0·008). Wheezing illness was associated with both antenatal (incidence rate ratio 2·09, 95% CI 1·54–2·84; p<0·0001) and postnatal (1·27, 95% CI 1·03–1·56; p=0·024) maternal smoking.

Antenatally, wheezing was associated with maternal passive smoke exposure (1·70, 1·25–2·31; p=0·001) and, postnatally, with any household member smoking (1·55, 1·17

–2·06; p=0·002).

Interpretation Antenatal exposures were the predominant risk factors associated with LRTI or wheezing illness. Toluene was a novel exposure associated with severe LRTI. Urgent and effective interventions focusing on antenatal environmental factors are required, including smoking cessation programmes targeting women of childbearing age pre-conception and pregnant women.

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1 Introduction

Lower respiratory tract illness (LRTI), principally pneumonia remains the leading cause of under-5 mortality in low and middle-income countries (LMIC), with a very high burden of disease in low and middle income country settings including Africa.[1] Wheezing illness is common in young children and asthma is the commonest non-communicable disease (NCD) in African children.[2] Indoor air pollution (IAP) or environmental tobacco smoke (ETS) exposure have been strongly associated with the development of childhood respiratory illness but there are little data on the impact of the timing of exposures on child respiratory health.[3,4]

Antenatally, in utero tobacco smoke exposure has been shown to affect lung growth and predispose to development of LRTI or wheezing disorders.[5] Potential mechanisms include the toxic effects of the numerous chemicals found in tobacco smoke on the developing respiratory system,[6] suppression of foetal breathing or direct genotoxicity,[7] the effects of nicotine on lung collagen deposition[6] and impaired immune function from imbalances in Th1 and Th2 responses.[8] While less clear, antenatal IAP exposure is postulated to impact lung development through an interplay of maternal and placenta-foetal factors including oxidative stress resulting in placental insufficiency with decreased transport of oxygen and nutrients to the developing foetus.[9] Postnatal IAP and/or ETS

exposure may disrupt pulmonary defences leading to epithelial inflammation, affect microbial colonisation and systemic inflammation, particularly if the alveolar capillary membrane is breached.[3] Most studies have focused on the association of postnatal IAP exposure on child respiratory health;[10] separating the impact of antenatal versus postnatal exposure is difficult with few studies able to delineate this.[9,11]

Many peri-urban communities, particularly in LMIC including South Africa are undergoing rapid urbanization. This has led to a shift in the type of IAP exposure with less use of open fires, but increasing use of cheap fuels such as paraffin, which produce volatile organic compounds (VOC) on combustion.[12] The impact of these on child respiratory health have not been well studied. Further there is a paucity of longitudinal African data, despite the high incidence of LRTI or wheezing illness,[13,14] large childhood populations and exposure to different forms of IAP and ETS.[15] The prevalence of ETS exposure is also underreported particularly in LMIC,[4] with most studies reporting cross sectional associations without objective measures of exposure and the extent and impact of exposures on child respiratory health has not been well studied especially in infants.

The aim of this study was to longitudinally investigate antenatal and postnatal exposure to IAP and/or ETS, using objective measurements, and the association with LRTI or wheezing illness in a South African birth cohort study.

2 Methods

2.1 Study population and procedures

A longitudinal study of children enrolled in the Drakenstein Child Health Study (DCHS), a birth cohort study,[16] in a peri-urban area of South Africa was done that included follow-up through the first year of life. Consecutive consenting pregnant women were enrolled at 20 – 28 weeks gestation at two public primary health clinics: Mbekweni (serving a predominantly black African population) and Newman (serving a predominantly mixed race population) from 1 March 2012 to 31 March 2015, a 3 year period so as to ensure constant enrolment over different seasons and time periods with more than 90% of the studied population attending the public health service[17] (Supplemental Table 1). Exclu-

sion criteria were individuals who were younger than 18 years, who did not attend study clinics for postnatal care (and thus could not be readily followed up), or those who were intending to move out of the district within 2 years after the infant's birth.[17] Study questionnaires and clinical data were collected at enrolment, and at follow up. All children were born at a central single hospital, Paarl hospital. Thereafter, mother-infant pairs were followed at 6-10 and 14 weeks, 6, 9 and 12 months. A composite socioeconomic status (SES) score was applied and participants categorized into quartiles as lowest, low-moderate, moderate-high or highest SES (Supplemental Table 1).[12,17,18]

2.2 Measuring exposure to IAP

An antenatal (within 4 weeks of enrolment) and postnatal (between 4-6 months of the infant's life) home visit was undertaken to assess the home environment and measure IAP. Dwellings were categorized[12] and the most common pollutants and by-products of combustion measured. Particulate matter (PM_{10}) was measured using a personal air sampling pump [SKC AirChek 52®] and carbon monoxide (CO) with an Altair® carbon monoxide single gas detection unit, left in homes for 24 hours. Diffusion tubes placed in homes for 2 weeks measured nitrogen dioxide (NO_2)/ sulphur dioxide (Radiello® adsorbent filters in polyethylene diffusive body) and volatile organic compounds (VOC), benzene and toluene, (Markes® thermal desorption tubes). As described previously an average concentration based on the 2-week duration in the home was obtained for nitrogen dioxide/sulphur dioxide and volatile organic compounds; 24-hour averages were obtained for particulate matter. Carbon monoxide data was downloaded to a computer and the frequency of exceedance above the hourly ambient standard was calculated. (Supplemental Table 1).[12] The South African National Ambient Air Quality Standards[19] were used to define expected exposure levels for each pollutant based on an averaging period of 1 year for each measure; PM_{10}: 40ug/m^3, NO_2: 40ug/m^3, benzene: 5ug/m^3, toluene: 240ug/m^3, CO: >30mg/m^3 (not more than 88 hours). (Supplemental Table 1).[19] During the postnatal home visit, these same measurements were repeated.

2.3 Measuring exposure to ETS

Questionnaires of maternal and paternal smoking and household exposure to tobacco smoke were administered at enrolment and at each follow-up visit during the antenatal and postnatal follow-up period.[20] Maternal exposure to ETS was also measured using urine cotinine, at the second antenatal visit (28-32 weeks gestation) and at birth with the highest result used to assign the mother's smoking status (Supplemental Table 1).[20] Urine cotinine levels were classified as <10 ng/ml (non-smoker), 10-499 ng/ml, (passive smoker/exposed), or ≥500 ng/ml (active smoker).[20]

2.4 Assessing lower respiratory tract disease

Respiratory disease was characterized as an episode of LRTI and/or wheeze. Study staff trained in the recognition of LRTI or wheezing illness documented all episodes either ambulatory or hospitalized. LRTI and severe LRTI were defined using World Health Organization (WHO) case definition criteria (Supplemental Table1).[13,21] Active surveillance for LRTI in the cohort was established (Supplemental Table1).[13] LRTI which occurred at or shortly after birth prior to discharge was defined seperately. Episodes of wheeze were self-reported by a caregiver at a study visit or diagnosed on auscultation by trained study staff at a study visit or inter-current illness. Study staff were trained in the recognition and auscultation of wheezing; caregivers were also trained in clinical recognition (Supplemental Table1). Recurrent wheezing was defined as 2 or more episodes of wheezing.

2.5 Ethics

The study was approved by the Faculty of Health Sciences Human Research Ethics Committees of the University of Cape Town and of Stellenbosch University, and by the Western Cape Provincial Health Research committee.

2.6 Statistical analysis

Data were analyzed using STATA 13·0 (STATA Corporation, College Station, TX USA). Simple descriptive statistics were used to characterize the study population, continuous data were summarized as median and interquartile range and categorical data were summarized as proportions with 95% confidence intervals (CI)s. Wilcoxon rank-sum test

was used to compare medians, and proportions were compared using the chi-squared test. Mixed effects Poisson regression clustered around the infant was used for multivariate analysis of LRTI incidence and multivariable Poisson regression for wheezing, results are presented as incidence rate ratios and 95% CIs. Univariate mixed effects logistic regression clustered around the infant was used to explore associations between demographic, household, socio-economic characteristics, indoor air pollutants and smoke exposure between severe vs non-severe LRTI, hospitalized vs ambulatory, LRTI requiring oxygen vs not requiring oxygen and wheeze at LRTI vs no wheeze in the subset of infants that had an LRTI; results are presented as odds ratios and 95% CIs. Univariate analysis tested the association between environmental and socio-economic factors and respiratory disease. (Supplemental Table1). Variables that were associated with these outcomes and those of clinical relevance were included in multivariate (mixed effects) logistic regression models to determine the effect of severity of disease. Wilcoxon signed-rank test was used to compare differences in the median pollutants measured antenatally to postnatally. Confounding variables (birth weight, gender, ethnicity (site), SES status, weight for age Z (WAZ) score,[22] maternal HIV status, crowding, household characteristics, fossil fuel usage, vaccination status, nutritional status and feeding in the first 6 months status) that showed an effect were included in the final analysis models (Supplemental Table1). All statistical tests were two-sided at $\alpha = 0{\cdot}05$.

2.7 Role of the funding source

The sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data and had final responsibility for the decision to submit for publication.

3 Results

Amongst 1137 mothers (median age 25.9 [IQR 22.1-30.8] years) enrolled with 1143 live births (4 sets of twins and 1 triplet), a total of 4521 visits were completed; 1065 children attended at least one of the study visits between birth and 12 months of age. Attendance varied at each time point with 1030 having attended the 6-10 week visit, 933 the 14 week visit, 936 the 6 month visit, 844 the 9 month visit and 778 the 12 month visit. A minority [119

(10%)] of children were lost to follow-up before the first full year of follow-up (Figure 1).

3.1 Demographics and home environment

There were notable differences between the Mbekweni (black African) and Newman (mixed ancestry) populations (Table 1). More black African participants were in the lowest SES quartile compared to mixed race participants; the median household size was lower 4 (IQR 3-6) versus 5 (IQR 4-7) for mixed race participants (Table 1). One-third of homes had less than two of the household dimensions, however, 94% of homes had access to electricity. Despite this 30% of black African homes used fossil fuels for cooking and heating (Table 1), with paraffin being used in 22% of homes. Twenty-two percent of infants were born to HIV-infected mothers and therefore HIV exposed, significantly more in black African infants (37% vs 3%), but only 2 infants were HIV infected. There were no differences between the maternal, household or birth characteristics of those included in the analysis or those lost to follow up except in the dwelling catergory where 244/1065 (38.8%) of homes had less than two household dimension compared to 37/119 (45.1%) in the LTFU group (p=0.018).

Birth weight for age Z-scores (WAZ) differed significantly with black African babies [median WAZ -0·41 (-1·22; 0·24)] heavier compared to mixed race babies [median WAZ -0·73 (IQR-1·36; -0·06)] (Table 1). Approximately 17% of all births were preterm, predominantly late preterm. Eighty-six percent of mother initiated breastfeeding, however, the median duration of exclusive breastfeeding was 2 (IQR 1-4) months. There was a high rate of infant vaccination including 13-valent pneumococcal conjugate vaccine, with above 80% coverage for the first 3 doses (Table 1).

3.2 IAP or tobacco smoke exposure

The median level of each of the pollutants measured did not exceed ambient standards.[19] The median PM_{10} level measured antenatally combining both sites was 33·12 (IQR 12·22 – 64·17) ug/m^3 significantly higher than the postnatal measurement of 29·29 (IQR 12·59 – 52·46), p=0·011. Of the VOC's, the median benzene concentration was significantly higher antenatally [4.29 (IQR 1·70 – 11·53) ug/m^3] compared to postnatal

[3·12 (IQR 1·09 – 9·46) ug/m^3] when both sites were combined, p=0·014. The median toluene concentration was 16·94 (IQR 7·05 – 44·85) ug/m^3 antenatally and 15·52 (IQR 5·93 – 49·95) ug/m^3 postnatally (Table 2). Use of paraffin for cooking was significantly associated with higher toluene values (p=0·04). When measures were compared between sites, at both antenatal and postnatal time points, only SO_2 (antenatally) and CO (postnatally) were significantly different (Supplemental Table 2).

Using antenatal maternal urine cotinine levels, 343/1058 (32%) mothers were active smokers and 464/1058 (44%) were exposed to tobacco smoke (Table 3). Smoking prevalence was significantly higher in mixed race (53%) compared to black African (15%) mothers p<0·001 (Table 3). Self-reported smoking correlated well with urine cotinine measurements, especially in mixed race women (Supplemental Table 3). There were high levels of reported smoke exposure to infants throughout the first year, with 41% of fathers, 22% of mothers and 37% of other household members reported to be smokers. In 74% of homes, at least one household member was reported as a smoker (Table 3).

3.3 Lower respiratory illness

3.3.1 LRTI

There were 569 cases of LRTI of which 45 (8%) occurred at or shortly after birth prior to discharge and analysed separately. Of 524 LRTI cases, more occurred amongst Black African (321, 61%) than mixed race (203, 39%) infants (p < 0·001). The median age at LRTI was 4·6 (IQR 2·8 – 7·4) months. The highest number of cases 178 (37%) occurred in winter. 105 (20%) were severe, and 137 (26%) required hospitalization. There were 5 (0.8%) LRTI-related deaths.

3.3.2 Wheeze

The overall prevalence rate for wheeze was 0·23 (95%CI 0·21 - 0·26) per child year, higher amongst mixed race [0·32 (95%CI 0·27-0·37)] compared to black African infants [0·16 (95%CI 0·13-0·20)], p<0·001. Recurrent wheeze occurred in 47 (4%) infants. Amongst LRTI cases, 227/524 (43%) had associated wheeze on auscultation (Table 4).

3.4 Association between antenatal environmental exposures and lower respiratory illness

3.4.1 LRTI: Antenatal exposures

Antenatal maternal smoking was associated with an increased risk of LRTI [IR 1·62 (95%CI 1·14-2·30)] as was male gender [IR 1·69 (95%CI 1·33 -2·13)]. Increasing infant age was associated with a decreased risk of LRTI (Table 5). Antenatal PM_{10} above ambient standards (>40ug/m^3) was significantly associated with LRTI [IR 1·43 (95% CI 1·06- 1·95)] (Table 5). In those children with LRTI, antenatal exposure to toluene above ambient standards (>240ug/m^3), was further associated with an almost five-fold increase in hospitalization, OR 5·13 (95% CI 1·43-18·36) (Supplemental Table 4) or with an increased requirement for oxygen; OR 13·21 (95% CI 1·96-89·16) (Supplemental Table 5). There were however, no significant exposures associated with WHO-defined severe LRTI, but the number of severe cases (n=44) meant the model was not sufficiently powered. There were no associations found between antenatal exposures and cases of congenital LRTI.

3.4.2 Wheezing illness: antenatal exposures

Antenatal maternal smoking increased the risk of infant wheezing, [IR 2·09 (95% CI 1·54-2·84)] as did passive smoke exposure [IR 1·70 (95% CI 1·25-2·31)] (Table 6). None of the IAP exposures were associated with an increased the risk of wheezing (Table 6). When correcting for both smoke exposure and IAP, a moderate-high SES [IR 1·53 (95% CI 1·17-2·00)] was associated with an increased risk of wheezing (Supplemental Table 9).

3.5 Association between postnatal environmental exposures and lower respiratory illness

3.5.1 LRTI: postnatal exposures

Neither postnatal self-reported maternal or household smoking nor PM_{10} exposure was associated with an increased risk of LRTI or of LRTI-associated hospitalization (Supplemental Tables 4 & 6).

3.5.2 Wheezing illness: postnatal exposures

None of the postnatal IAP measured were associated with wheeze but postnatal maternal smoking IR 1·27 (95% CI 1·03 –1·56) and any household member smoking IR 1·55 (95% CI 1·17 –2·06) was associated with an increased risk of infant wheezing; (Supplemental Table 7).

3.6 Combined antenatal and postnatal exposures

Although combined antenatal and postnatal ETS exposure increased the risk of wheezing [IR 1·79 (95% CI 1·34 -2·38)], this was similar to the risk associated with antenatal exposure alone (Supplemental Table 8). Further, combined ETS and IAP exposure increased the risk of wheezing [IR 1·96 (95% CI 1·32-2·92)], however this was also similar to the risk associated with either ETS or IAP exposure (Supplemental Table 9).

Combining antenatal and postnatal ETS exposure or combined IAP exposure was not associated with a risk of LRTI (Supplemental Tables 8 & 9).

4 Discussion

A high incidence of LRTI or wheezing illness was found in infants in this poor peri-urban community, associated with very high rates of exposure to tobacco smoke and IAP. Antenatal exposures were much more strongly associated with respiratory disease in the first year of life with maternal smoking, ETS exposure, PM_{10} or toluene exposure associated with LRTI, wheezing or hospitalization for respiratory illness. Amongst postnatal exposures, only maternal smoking was associated with an increased risk of wheezing in infants. Recurrent wheezing was unusual, as might be expected in the first year of life.

The effect of antenatal ETS exposure may relate to high levels of in utero exposure with higher levels than those occurring postnatally. This is consistent with our findings in this cohort, in which infant urine cotinine levels at birth attain levels equivalent to an active smoker in babies born to mothers who smoke, but reduce at 6-10 weeks of age to levels indicative of passive exposure associated with maternal smoking.[20] Further, antenatal exposure may occur at a crucial time of lung development, impairing lung growth.[7] In vi-

tro studies have shown that nicotine impairs lung growth and increases collagen deposition in airways.[6] The very high prevalence of maternal smoking in pregnancy, particularly in the mixed race population (53%), which was up to 10 times higher than the reported African pooled prevalence,[23] and high exposure to tobacco smoke in utero are concerning. The results may not be generalizable to settings with lower levels of smoke exposure; however, maternal smoking prevalence is rising in Africa and amongst pregnant women[23]. Further self-reported smoking is under reported by pregnant women; however in our study self-reported smoking and urine cotinine measurements correlated closely especially in the mixed race, high prevalence smoking community.

A few studies have tried to differentiate timing of exposure on the development of childhood respiratory illness[24,25] with difficulty in measuring the impact of antenatal compared to postnatal exposure. In this study antenatal exposure was the most important risk associated with the development of respiratory illness in infants.

The differences between antenatal and postnatal measurements of particulate matter (PM_{10}) were due to a combination of seasons and sites. Antenatal exposure to particulate matter (PM_{10}) was associated with an increased risk of LRTI, as has been previously reported.[10,26,27] This may be due to impaired lung growth and increased risk of infection associated with exposure.[28] Further, innate immune responses may be compromised due to impairment of alveolar macrophage function and upregulation of inflammatory responses.[29-31] Particulate matter inhaled during pregnancy may therefore act directly on the developing fetus or induce a systemic immune or inflammatory response resulting in placental insufficiency leading to reduced fetal oxygen and nutrients.[9,32] By comparison postnatal exposure relies on direct inhalation of PM that results in increased number of macrophages, neutrophils and T lymphocytes in the lungs.[30] The antenatal developmental factors increased the susceptibility to LRTI more than postnatal exposure, particularly in in the first months of life.

A novel finding was the association between antenatal toluene exposure and severe LRTI, with exposure increasing the risk of hospitalization almost five-fold and the need for supplemental oxygen more than thirteen-fold. Toluene, a VOC, has numerous sourc-

es including ETS, paraffin, solvents, emissions and household products,[33] reflective of the sources of IAP in many poor peri-urban communities. Although toluene exposure has been reported to play a role in wheezing illnesses and asthma development or exacerbations, no studies have described the association of antenatal toluene exposure with LRTI in children.[34,35] Consistent with the findings for other IAP exposures, postnatal exposure was not associated with LRTI incidence or severity. In vitro studies, have shown an effect on immune cells including suppression of cytokine secretion and lymphocyte activity, so potentially increasing susceptibility to severe LRTI.[36] Further, antenatal maternal exposure to IAP may affect the developing fetal innate immune system in particular toll-like receptor and nucleotide-binding oligomerization domain–like receptor involved in pathogen-induced immune responses,[37] which may contribute to the severity of LRTI as occurred in infants with antenatal toluene exposure. Mice models have also shown a shift in balance from Th1/Th2 to predominantly Th2 responses with toluene exposure.[38] While the small number of severe cases of LRTI may be a limitation of this observation, this association requires further investigation, particularly as VOC exposures are ubiquitous, increasing globally and often under-recognized.

The incidence of LRTI and prevalence of wheezing was high, with important differences in the two communities. While LRTI was more common in black African infants, wheezing was more prevalent in mixed race infants, even though more than 40% of LRTI was associated with wheezing. The higher prevalence of wheezing in mixed race infants may be explained by high exposure to ETS from antenatal maternal smoking and household smoking. The higher prevalence of LRTI in black African infants may be explained by their poorer socioeconomic status, with more homes lacking basic household dimensions, higher HIV exposure and associated household exposure to potential pathogens or greater use of fossil fuels for cooking and heating.[12] The effects of other recognized risk factors associated with LRTI including crowding, nutritional status and immunization were explored but no significant associations were found. However, immunization rates in both communities was high and nutrition was generally good.

Strengths of this study include the longitudinal follow up, prospective collection of data, high cohort retention and repeated objective measures of IAP and ETS through the

antenatal period and through infancy. Few studies, particularly from LMIC have directly measured household IAP exposures in large numbers.[39] The strong association between antenatal exposures and LRTI including severe LRTI, which did not occur with postnatal exposures, suggests that in utero exposures may be important in determining susceptibility to LRTI in infancy. This may be mediated through effects on lung function, as we have previously shown that antenatal smoke exposure is associated with lower lung function and lower respiratory system compliance in these infants shortly after birth.[40,41] Limitations of this study include the broad clinical definition of LRTI used, however the WHO definitions are widely used for maximum sensitivity and to reflect the broad spectrum of LRTI. A further limitation was reliance on caregiver report of wheezing episodes; however, physician diagnosed wheezing also occurred at follow-up or sick visits and at the time of LRTI. Further, large epidemiological studies such as the International Study of Asthma and Allergies in Childhood have relied on report of wheeze as a standard method.[2] Other limitations were the use of maternal rather than infant birth urine cotinine measures to assess ETS exposure, given that not all infants had urine collected at birth and a lack of validated post-natal measures of ETS exposure. However, maternal self report and urine cotinine levels were highly correlated as was the sensitivity of self-reported household smokers compared to cotinine results.[20]

Antenatal exposures were the most significant exposures associated with LRTI in infancy suggesting a developmental lung effect. This study highlights the need for urgent and effective smoking cessation programmes targeting women of child bearing age pre-conception and of pregnant women. The study also highlights the importance of other sources of IAP including toluene exposure, which has not been previously described to be associated with severe LRTI, and which are increasingly used as rapid urbanisation in LMICs occurs. Limiting IAP exposure, by identifying household sources of IAP and providing safe alternative fuels, and improving household ventilation[39,42] may be important strategies to optimize child health. The study underscores the importance of the antenatal period as a time of exposure, in contrast to the postnatal period, which has been the focus of most studies. Further study of this cohort will provide important information on the long-term effects of these exposures on respiratory health in a LMIC population.

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Figure 1: Trial profile

The trial profile shows the number of eligible infants assessed at each visit, excluding those who did not attend that specific visit. Eligibility at each visit is defined as all infants minus the total number of infants lost to follow-up by that visit. All infants who attended at least one study visit were assessed, including those lost to follow-up who had attended at least one visit

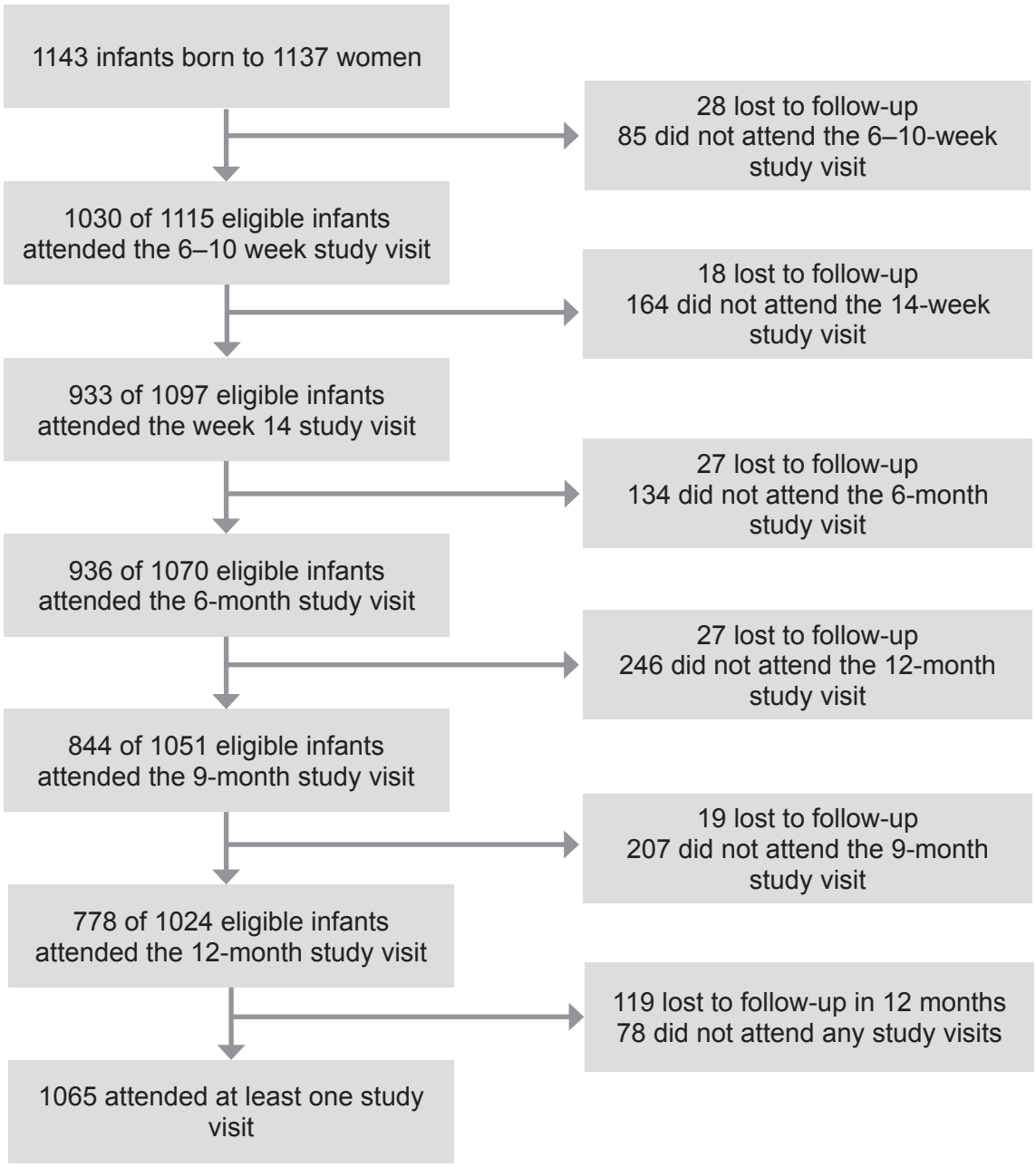

Table 1: Demographic characteristics of the cohort and antenatal home environment

	Mbekweni N (%)	Newman N (%)	Total N (%)	P value
Baseline Characteristics				
Number of mothers	583 (55%)	477 (45%)	1060	
Age at enrolment	26.9 [22·5-31·7]	24·8 [21·4-29·2]	25·9 [22·1-30·8]	<0·001
Number of infants	588 (55%)	477 (45%)	1065	
Male	288 (49%)	260 (55%)	548 (51%)	0·073
Preterm * (Gestation median 35 (IQR 32-36) weeks)	100 (17%)	75 (16%)	175 (16%)	0·574
Birth WAZ (Adjusted for gestation)	-0·41 (-1·22, 0·24)	-0·73 (-1·36, -0·06)	-0·54 (-1·31, 0·09)	<0·001
HIV exposure	219 (37%)	16 (3%)	235 (22%)	<0·001
Initiated breast feeding	430 (78%)	448 (96%)	878 (86%)	<0·001
Duration of exclusive breast feeding Median (IQR) months	2·00 (1·00, 3·65)	2·00 (1·00, 4·00)	2·00 (1·00, 4·00)	0·766
Ethnicity				
Black	581 (99%)	6 (1%)	587 (55%)	<0·001
Mixed / other	7 (1%)	471 (99%)	478 (45%)	
Vaccinations Received				
1st dose (EPI at 6 weeks)				
Received on time	484/529 (91%)	404/438 (92%)	888/967 (92%)	0·485
Received 2 weeks late	32/529 (6%)	32/438 (7%)	64/967 (7%)	
2nd dose (EPI at 10 weeks)				
Received on time	438/520 (84%)	368/433 (85%)	806/953 (85%)	0·273
Received 2 weeks late	70/520 (13%)	64/433 (15%)	134/953 (14%)	
3rd dose (EPI at 14 weeks)				

Received on time	510/512 (99·6%)	421/422 (100)	931/934 (99·6%)	0·199
Received 2 weeks late	2/512 (0·4%)	0/422 (0)	2/934 (0·4%)	
4th dose (EPI at 9 months)				
Received on time	385/471 (82%)	289/380 (76%)	674/851 (79%)	0·011
Received 2 weeks late	74/471 (16%)	87/380 (23%)	161/851 (19%)	
SES quartiles N (%)				
Lowest SES	176 (30%)	85 (18%)	261 (25%)	<0·001
Low-mod SES	164 (28%)	117 (25%)	281 (26%)	
Mod-high SES	137 (23%)	134 (28%)	271 (25%)	
High SES	111 (19%)	141 (30%)	252 (24%)	
Household Density Median (IQR)				
Household size	4·0 (3·0, 6·0)	5·0 (4·0, 7·0)	4·0 (3·0, 6·0)	<0·001
Persons per room	2·0 (1·0, 2·0)	1·0 (1·0, 2·0)	2·0 (1·0, 2·0)	0·004
Persons per sleeping room	3·0 (2·0, 4·0)	3·0 (2·0, 5·0)	3·0 (2·0, 4·0)	<0·001
Dwelling category †‡ N (%)				
Has ≤2 dimensions	164 (39%)	98 (26%)	262 (33%)	<0·001
Has ≥2 dimensions	257 (61%)	277 (74%)	534 (67%)	
Electricity Access	535 (91%)	3465 (98%)	1000 (94%)	<0·001
Fossil fuel (coal, wood, paraffin, gas) used† N (%)				
Cooking	133 (32%)	35 (9%)	168 (21%)	<0·001
Heating	129 (31%)	6 (2%)	135 (17%)	<0·001

IQR, inter-quartile range; WAZ, weight-for-age z-score; HAZ, height-for-age z-score; HIV, human immunodeficiency virus; EPI, Expanded Programme on Immunisation; SES, socio-economic status.

*Median gestation for preterm infants in the study was 35 weeks (IQR 32–36).

†Home assessments of dimensions and fossil fuel use were successfully completed for 796 of the 1060 homes.

‡The six dwelling dimensions were type of home (formal vs informal), primary building material (brick or cement vs other materials), water supply (piped into dwelling or yard), toilet facilities (noncommunal flush), kitchen type (separate room in house), and ventilation in the kitchen area (pipe or duct to exterior).

Table 2: Measured indoor air pollution (IAP) exposure at antenatal and postnatal home visits

IAP Measure ***Ambient Concentration***	**Antenatal** ***Median (IQR)***	**Postnatal** ***Median (IQR)***	**P Value**
Particulate Matter (PM_{10}) (ug/m^3)	33·12 (12·22 - 64·17)	29·29 (12·59 - 52·46)	0·011
Nitrogen Dioxide (ug/m^3)	7·08 (3·32 - 12·70)	5·83 (2·58 - 12·55)	0·812
Sulphur Dioxide (ug/m^3)	0·00 (0·00 - 0·28)	0·00 (0·00 - 0·00)	0·058
Benzene (ug/m^3)	4·29 (1·70 - 11·53)	3·12 (1·09 - 9·46)	0·014
Toluene (ug/m^3)	16·94 (7·05 - 44·85)	15·52 (5·93 - 49·95)	0·869
Average Carbon Monoxide Per Hour (mg/m^3)	0·00 (0·00 - 7·65)	0·00 (0·00 - 0·00)	0·923

Note: Calculated based on matched pairs. (Based on Wilcoxon signed rank test)

Table 3: Tobacco smoking and environmental tobacco smoke exposure by study site

	Mbekweni (black African) N (%)	Newman (mixed race) N (%)	Total N (%)	P value
Antenatal tobacco smoke exposure (urine cotinine)				
Number of mothers	574	484	1058	
Urine cotinine <10 ng/ml (Non-smoker)	195 (34·0%)	56 (11·6%)	251 (23·7%)	< 0·001
Urine cotinine 10-499 ng/ml (Passive / exposed)	291 (50·7%)	173 (35·7%)	464 (43·9%)	
Urine cotinine ≥500 ng/ml (Active smoker)	88 (15·3%)	255 (52·7%)	343 (32·4%)	
Self-reported smoking during infancy				
Number of participants	583	477	1060	
Mother	43 (8·7%)	280 (29.2%)	323 (22.2%)	< 0·001
Father	271 (54·7%)	320 (33.4%)	591 (40.7%)	
Other household members	181 (36·6%)	358 (37.4%)	539 (37.1%)	
Total number of household smokers				
Number of participants	583	477	1060	
None	239 (41·0%)	41 (8·6%)	280 (26·4%)	<0·001
One	208 (35·7%)	87 (18·2%)	295 (27·8%)	
Two	121 (20·8%)	176 (36·9%)	297 (28·0%)	
> Three	15 (2·6%)	173 (36·3%)	188 (17·7%)	

Table 4: Wheezing in infants at follow-up study visits and cumulative wheeze at 1 year

	Monthly Visits											
	6 - 10 weeks N = 1030		**14 weeks N = 933**		**6 months N = 936**		**9 months N = 844**		**12 months N = 778**		**Cumulative N=1065**	
Visit numbers by site	MK	NM	MK	NM	MK	NM	MK	NM	MK	NM	MK	NM
	560	470	504	429	503	433	436	408	397	381	480	424·2
Caregiver reported wheeze total, N (%)	53 (5·2)		45 (5·0)		56 (6·0)		36 (4·3)		64 (8·2)		212 (20% of 1065)	
Caregiver reported wheeze by site, N (%)	MK	NM	MK	NM	MK	NM	MK	NM	MK	NM	MK	NM
	22 (4·0)	31 (6·6)	17 (3·4)	28 (6·5)	19 (3·8)	37 (8·6)	7 (1·6)	29 (7·1)	19 (4·8)	45 (11·8)	77 (13·1)	135 (28·3)
Treated for wheeze, N (%)	27 (51·0)		21 (47·7)		37 (67·3)		20 (55·6)		43 (72·9)		129 (60·8% of 212)	
Prevalence rate (95% CI) per visit	0·05 (0·03 - 0·07)		0·05 (0·04 - 0·06)		0·06 (0·05 - 0·08)		0·04 (0·03 - 0·06)		0·08 (0·06 - 0·10)		0·23 (0·21 - 0·26) *	
Recurrent wheeze (≥ 2 episodes), N (%)	4 (0·4)		14 (1·5)		15 (1·6)		10 (1·2)		6 (0·8)		47 (4% of 1065)	
* Cumulative prevalence rate (95% CI) per visit: MK 0·16 (0·13-0·20); NM 0·32 (0·27-0·37) p<0·001												

MK, MMK, Mbekweni; NM, Newman

Table 5 Multivariate analysis for lower respiratory tract illness (LRTI) and antenatal environmental exposures

Tobacco Smoke Exposure (N = 1059)		
	IRR (95% CI)	**P value**
Site		
Mbekweni	1·43 (1·07 - 1·90)	0·009
Maternal smoke status		
Active smoker	1·62 (1·14 -2·30)	0·004
Passive smoker	1·04 (0·76 - 1·41)	0·483
Infant characteristics		
Male	1·69 (1·33 - 2·13)	<0·001
WAZ at birth	0·96 (0·86 - 1·06)	0·239
Maternal HIV exposure	1·12 (0·83 - 1·50)	0·488
Age in months	0·90 (0·88 - 0·92)	<0·001
SES quartiles		
Lowest SES	1·12 (0·79 - 1·59)	0·485
Low-mod SES	1·42 (1·02 - 1·97)	0·042
Mod-high SES	0·98 (0·70 - 1·39)	0·918
Indoor Air Pollutant Exposure (N = 763)		
	IRR (95% CI)	**P value**
Site		
Mbekweni	1·02 (0·76 - 1·36)	0·872
Indoor air pollutant exposure		
PM_{10} above ambient standard	1·43 (1·06 - 1·95)	0·008
Infant characteristics		
Male	1·76 (1·34 - 2·31)	<0·001
WAZ at birth	0·89 (0·79 - 1·00)	0·063
Maternal HIV exposure	1·02 (0·72 - 1·46)	0·833
Age in months	0·91 (0·89 - 0·94)	<0·001
SES Quartiles		
Lowest SES	1·15 (0·78 - 1·69)	0·324
Low-mod SES	1·46 (1.01 - 2·12)	0·039
Mod-high SES	0·99 (0·67 - 1·47)	0·885

WAZ, weight-for-age z-score; HIV, human immunodeficiency virus; SES, socio-economic status; PM_{10}, particulate matter

Table 6: Multivariable analysis for infant wheezing and antenatal environmental exposures

Smoke Exposure (N = 830)		
	IRR (95% CI)	**P value**
Maternal smoke status		
Active smoker	2·09 (1·54 – 2·84)	<0·001
Passive smoker	1·70 (1·25 – 2·31)	0·001
Infant characteristics		
Male	1·41 (1·16 - 1·72)	0·001
WAZ at birth	0·98 (0·89 – 1·07)	0·614
Maternal HIV exposure	0·49 (0·33 - 0·72)	<0·001
SES quartiles		
Lowest SES	0·95 (0·70 - 1·30)	0·760
Low-mod SES	1·23 (0·93 - 1·63)	0·151
Mod-high SES	1·51 (1·15 – 1·98)	0·003
Infant feeding		
Duration exclusively breast fed in months	0·98 (0·93 - 1·03)	0·435
Indoor Air Pollutant Exposure (N = 585)		
	IRR (95% CI)	**P value**
Indoor air pollution		
Toluene above ambient standard	1·29 (0·88 – 1·89)	0·197
Particulate Matter (PM_{10}) above ambient standard	0·93 (0·70 - 1·25)	0·643
Benzene above ambient standard	1·08 (0·85 - 1·38)	0·539
Infant characteristics		
Male	1·50 (1·19 – 1·91)	0·001
WAZ at birth	0·95 (0·85 - 1·06)	0·327
Maternal HIV exposure	0·55 (0·34 – 0·90)	0·018
SES quartiles		
Lowest SES	0·99 (0·67 – 1·45)	0·942
Low-mod SES	1·51 (1·07 – 2·13)	0·019

Mod-high SES	1·62 (1·15 – 2·27)	0·006
Infant feeding		
Duration exclusively breast fed in months	0·99 (0·93 - 1·05)	0·740

WAZ, weight-for-age z-score; HIV, human immunodeficiency virus; SES, socio-economic status
*Site excluded as significant confounder

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Supplemental information

Early-Life Exposure to Indoor Air Pollution or Tobacco Smoke and Lower Respiratory Illness in African Infants.

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Supplemental Table 1: Methods

Study population and procedures	
1.1 Health Facilities	Mbekweni and Newman health facilities provide free primary health to women and children, including antenatal care, a strong prevention of mother to child transmission (PMTCT) HIV program, childhood immunizations including thirteen valent pneumococcal conjugate vaccine (PCV13) and care for intercurrent illness. Hospital referral is to the single public hospital serving the area, Paarl hospital.
1.2 Sociodemographic	Sociodemographic data were collected using a questionnaire adapted from the South African Stress and Health Study (SASH).(1) A composite SES score was developed based on current employment status and standardised scores of educational level, household income and a composite asset index made up of access to household resources, amenities and market access categorising participants as being lowest SES, low-moderate SES, moderate-high SES or high SES.
Measuring exposure to IAP	
1.3 Dwelling categorization	Dwellings were catergorized as a poor structure if there were 2 or less of 6 dwelling dimensions (type of home, building material, water supply, type of toilet, kitchen type and ventilation).(2)e An implementation of the Alkire-Foster method, a flexible technique used to incorporate a number of dimensions of poverty or well-being, that can complement poverty assessment (2, 3) was applied to the dwelling characteristics. Six dwelling factors were used; type of home (formal versus informal), primary building material (brick or cement versus other materials), water supply (piped into dwelling or yard), toilet facilities (non communal flush), kitchen type (separate room in house) and ventilation in the kitchen area (pipe or duct to exterior). Dwellings were then categorised according to the number of dimensions lacking. This method defines a dwelling as a “poor structure” if it lacks one-third or more of the factors considered.(4)
1.4 Pollutant measurement equipment	• Particulate matter (PM_{10}) (personal air sampling pump – SKC Aircheck 52®) • Carbon monoxide (CO) (Altair^{R} Carbon Monoxide single gas detection unit) • Nitrogen dioxide (NO) and sulphur dioxide (Radiello^{R} adsorbent filters in polyethylene diffusive body) • Volatile organic compounds (VOC) benzene and toluene (Markes^{R} thermal desorption tubes using passive diffusion tubes).(4) • All measurements were done in the communal/main living room, away from windows and doors, approximately 1.5 meters from the ground.
1.5 National Ambient Air Quality Standards	Expected exposure for each pollutant based on an averaging period of 1 year for each measure; PM_{10}: 40ug/m^3, NO_2: 40ug/m^3, benzene: 5ug/m^3, toluene: 240ug/m^3, CO: >30mg/m^3 (not more than 88 hours). (5) An average concentration based on the 2-week duration in the home was obtained for sulphur dioxide/nitrogen dioxide and volatile organic compounds; 24-hour averages were obtained for particulate matter. Carbon monoxide data was downloaded to a computer and the frequency of exceedance above the hourly ambient standard was calculated. Based on the 10 minute readings, total hourly concentrations were computed using the trapezium rule. Two consecutive ten minute CO readings were used to represent parallel sides of a trapezium and the 10 minute interval to represent the distance between the parallel sides (width). The trapezium formula; half the sum of the parallel sides multiplied by the width, was then applied. The sum of six consecutive trapezia areas to represent total CO concentration in an hour was then calculated. Using this approach hourly concentrations were then determined for the entire duration of the CO device in the household. (4)

Measuring exposure to ETS	
1.6 Self-reported exposure	Maternal tobacco smoking and exposure were assessed using detailed self report questionnaires at enrolment. Post-natal follow-up questionnaires on child respiratory health included questions on tobacco smoke exposure from partners and household members. Maternal smoking was quantified as pack years, where one pack year was defined as 20 cigarettes smoked daily for one year. Maternal nicotine dependence was assessed using the Fagerström test for nicotine dependence, a well-validated questionnaire which scores tobacco dependence as low, low to moderate, moderate or high. The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) was administered to assess substance use and substance-related risk.(6)
1.7 Urine cotinine measurement	Urine cotinine tests were performed using the IMMULITE® 1000 Nicotine_Metabolite Kit (Siemens Medical Solutions Diagnostics^{R}, Glyn Rhonwy, United Kingdom) (7)
Assessing lower respiratory disease	
1.8 WHO pneumonia/LRTI case definitions	WHO pneumonia/LRTI case definition: cough or difficulty breathing and age-specific tachypnea or lower chest wall in-drawing).(8) WHO severe pneumonia/LRTI case definition: any child under 2 months of age with signs of pneumonia/LRTI or in a child of any age with danger signs (cyanosed, unable to drink, seizures, or decreased level of consciousness).(8, 9)
1.9 Surveillance for pneumonia/LRTI	Active surveillance for pneumonia/LRTI in the cohort was undertaken as described, using community field workers, a short message system (SMS) phone system, ongoing monitoring of cases at health facilities and study staff who could be contacted by a mother at all times.(10)
1.10 Recognition of LRTI/wheezing	Child caregiver reports at each study visit and episodes identified through the active surveillance for respiratory symptoms associated with LRTI was used to measure wheeze. Study nurses at the primary clinics performed active surveillance and assessed presenting infants in real time. (10, 11) Training of nursing staff included video-clips demonstrating clinical signs. The study doctor provided regular on-site refresher training and competency assessment.(10)
Statistical analysis	
1.11 Confounding variables	Potential confounding variables included birth weight, gender, ethnicity (site), SES status, weight for age Z (WAZ) score,(12) maternal HIV status, crowding, household characteristics, fossil fuel usage, vaccination status, nutritional status and feeding in the first 6 months status.

Supplemental Table 2: Indoor air pollution (IAP) measurements recorded at antenatal and postnatal visits

	Antenatal				Postnatal			
IAP Measure Ambient Concentration	**Mbekweni Median (IQR)**	**Newman Median (IQR)**	**All Median (IQR)**	**P Value**	**Mbekweni Median (IQR)**	**Newman Median (IQR)**	**All Median (IQR)**	**P Value**
Particulate Matter (PM_{10}) (ug/m^3)	31·77 (12·36 - 62·73)	36.04 (13.01 - 65·84)	33·41 (12·49 - 64·80)	0·348	30·29 (14·67 – 51·05)	28·44 (10·47 - 53·71)	29·47 (12·59 - 52·48)	0·328
Nitrogen Dioxide (ug/m^3)	6·87 (2·50 - 14·56)	7·12 (3·84 - 11·28)	7·03 (3·31 - 12·66)	0·622	6·34 (2·81 - 14·57)	5·28 (2·48 - 11·25)	5·83 (2·58 - 12·55)	0·130
Sulphur Dioxide (ug/m^3)	0·00 (0·00 - 0·34)	0·00 (0·00 - 0·17)	0·00 (0·00 - 0·28)	0·039	0·00 (0·00 - 0·00)	0·00 (0·00 - 0·00)	0·00 (0·00 - 0·00)	0·794
Benzene (ug/m^3)	4·50 (1·46 - 17·71)	3·88 (1·83 - 8·56)	4·28 (1·74 - 11·39)	0·637	2·81 (0·75 - 14·41)	3·22 (1·46 - 7·57)	3·08 (1·06 - 9·46)	0·312
Toluene(ug/m^3)	16·06 (5·84 - 42·92)	17·54 (8·24 - 46·48)	16·88 (7·04 - 44·57)	0·213	14·72 (4·79 - 48·77)	15·89 (6·52 - 51·66)	15·50 (5·90 - 48·97)	0·286
Average Carbon Monoxide Per Hour (mg/m^3)	0·00 (0·00 - 3·22)	0·00 (0·00 - 9·09)	0·00 (0·00 - 6·21)	0·105	0·00 (0·00 - 0·00)	0·00 (0·00 - 5·57)	0·00 (0·00 - 0·00)	0·015

IAP, indoor air pollution; IQR, inter-quartile range

Supplemental Table 3: Correlation of maternal antenatal cotinine and self-reported total smoke exposure

	Mbekweni		Newman		All	
	Sensitivity	**Specificity**	**Sensitivity**	**Specificity**	**Sensitivity**	**Specificity**
Estimate, %	71·30	59·00	95·40	35·70	83·60	53·80
95% Confidence Interval, %	66·80 – 75·50	51·70 – 66·00	93·00 – 97·10	23·40 – 49·60	81·00 – 86·00	47·40 – 60·10

Supplemental Table 4: Risk factors for lower respiratory tract illness (LRTI) requiring hospitalization

	Antenatal Risk Factors						**Postnatal Risk Factors**					
	All Episodes N = 524		**Included in Model N = 245**		**OR (95%CI)**	**P value**	**All Episodes N = 524**		**Included in Model N = 127**		**OR (95%CI)**	**P value**
	Amb., N = 387	Hsp., N =137	Amb., N = 177	Hsp., N = 68	OR (95%CI)	P value	Amb., N = 387	Hsp., N =137	Amb., N = 100	Hsp, N = 27	OR (95%CI)	P value
Site												
Mbekweni	251 (65%)	73 (53%)	82 (46%)	27 (40%)	0·77 (0·35 - 1·72)	0.524	251 (65%)	73 (53%)	50 (50%)	12 (44%)	0·40 (0·10 - 1·66)	0206
Smoke exposure status												
Antenatal maternal non-smoker	75 (19%)	22 (16%)	36 (20%)	14 (20%)	1							
Antenatal / Postnatal maternal active smoker	134 (35%)	61 (45%)	70 (40%)	31 (46%)	0·67 (0·28 - 1·60)	0·362	109 (28%)	50 (37%)	33 (33%)	12 (44%)	1·12 (0·23 - 5·45)	0·893

	Antenatal Risk Factors						Postnatal Risk Factors					
	All Episodes N = 524		**Included in Model N = 245**		**OR (95%CI)**	**P value**	**All Episodes N = 524**		**Included in Model N = 127**		**OR (95%CI)**	**P value**
Antenatal maternal passive smoker / Postnatal household smoker	158 (41%)	44 (32%)	71 (40%)	23 (34%)	0·58 (0·23 - 1·50)	0·264	269 (70%)	101 (74%)	77 (77%)	21 (78%)	0·50 (0·12 - 2·19)	0·359
Unknown	20 (5%)	10 (7%)										
Infant characteristics												
Gender (male)	240 (62%)	91 (66%)	123 (69%)	50 (74%)	1·05 (0·52 - 2·11)	0·887	240 (62%)	91 (66%)	64 (64%)	20 (74%)	2·10 (0·64 - 6·97)	0·223
WAZ at birth	-0·7 (-1·4, -0·1)	-0·8 (-1·5, 0·0)	-0·8 (-1·5, -0·1)	-0·9 (-1·6, 0·0)	0·64 (0·51 - 0·82)	<0·001	0·2 (-0·6, 1·1)	-0·4 (-1·7, 0·8)	0·6 (-0·3, 1·3)	0.0 (-0·6, 0·9)	1·06 (0·60 - 1·89)	0·836
Maternal HIV exposure	107 (28%)	39 (28%)	22 (12%)	13 (19%)	2·04 (0·76 - 5·45)	0·156	107 (28%)	39 (28%)	9 (9%)	7 (26%)	11·14 (1·71 - 72·73)	0·012
Age (mid-interval in days)	4·7 (3 - 7)	2·5 (1·5 - 7)	5·2 (3·3 - 7·1)	2·9 (1·5 - 8·1)	0·90 (0·82 - 1·00)	0·050	4·7 (3 - 7)	2·5 (1·5 - 7)	5·2 (3·3 - 7·1)	2·3 (1·5 - 8·4)	0·89 (0·74 - 1·07)	0·215
SES quartiles (compared to high SES)												
Lowest SES	96 (25%)	37 (27%)	47 (27%)	15 (22%)	0·56 (0·22 - 1·42)	0·221	96 (25%)	37 (27%)	35 (35%)	10 (37%)	0·75 (0·21 - 2·65)	0·659

	Antenatal Risk Factors						Postnatal Risk Factors					
	All Episodes N = 524		Included in Model N = 245		OR (95%CI)	P value	All Episodes N = 524		Included in Model N = 127		OR (95%CI)	P value
Low-mod SES	139 (36%)	40 (29%)	64 (36%)	23 (34%)	0·99 (0·41 - 2·37)	0·977	61 (16%)	19 (14%)	17 (17%)	5 (19%)	0·60 (0·14 - 2·53)	0·490
Mod-high SES	83 (21%)	31 (23%)	36 (20%)	12 (18%)	0·75 (0·28 - 1·97)	0·558	74 (19%)	20 (14%)	25 (25%)	3 (11%)	0·27 (0·05 - 1·34)	0·109
High SES	69 (18%)	29 (21%)	30 (17%)	18 (26%)	1		59 (15%)	24 (18%)	23 (23%)	9 (33%)	0·27 (0·05 - 1·34)	
Unknown							97 (25%)	37 (27%)			0·27 (0·05 - 1·34)	
Method of feeding												
Duration of exclusive breast feeding (months)	2.0 (1.0 - 3·4)	2.0 (1.0 - 4.0)	2.0 (1.0 - 3·2)	1·7 (1.0 - 4.0)	0.95 (0·79 - 1·14)	0·577	2.0 (1.0 - 3·4)	2.0 (1.0 - 4.0)	1·9 (1.0 - 5.0)	1·5 (1.0 - 3.0)	0·86 (0·64 - 1·15)	0·304
Toluene indoor air pollution												
Below ambient standard	223 (58%)	76 (55%)	172 (97%)	61 (90%)	1		125 (32%)	41 (30%)	88 (88%)	22 (81%)	0·86 (0·64 - 1·15)	
Above ambient standard	8 (2%)	7 (5%)	5 (3%)	7 (10%)	5·13 (1·43 - 18·36)	0·012	17 (4%)	5 (4%)	12 (12%)	5 (19%)	1·63 (0·40 - 6·70)	0·500
Unknown	156 (40%)	54 (40%)					245 (64%)	91 (66%)			(0·64 - 1·15)	

WAZ, weight-for-age z-score; HIV, human immunodeficiency virus; SES, socio-economic status; Amb., ambulatory; Hsp., hospitalized

Supplemental Table 5: Risk factors for lower respiratory tract illness (LRTI) requiring oxygen

	Antenatal Risk Factors						Postnatal Risk Factors					
	All Episodes N = 524		Included in Model N = 244				All Episodes N = 521		Included in Model N = 127		OR (95% CI)	P value
	No Oxygen N = 452	Oxygen N = 69	No Oxygen N = 209	Oxygen N = 35	OR (95%CI)	P value	No Oxygen N = 452	Oxygen N = 69	No Oxygen N = 116	Oxygen N = 11	OR (95%CI)	P value
Site												
Mbekweni	285 (63%)	36 (52%)	90 (43%)	18 (51%)	1·57 (0·49 - 5.00)	0·446	285 (63%)	36 (52%)	58 (50%)	4 (36%)	0·06 (0·0 - 21·10)	0·346
Smoke exposure status												
Antenatal maternal non-smoker	85 (19%)	10 (14%)	43 (21%)	7 (20%)	1·0							
Antenatal passive smoker (cotinine)	178 (39%)	23 (33%)	78 (37%)	15 (43%)	1·34 (0·36 - 4·92)	0·659						
Antenatal active smoker (cotinine)	166 (37%)	29 (42%)	88 (42%)	13 (37%)	1·03 (0·25 - 4·34)	0·966						
Postnatal maternal smoker							136 (30%)	23 (33%)	41 (35%)	4 (36%)	1·78 (0·03 - 96·25)	0·778
Postnatal household smoker							319 (71%)	48 (70%)	90 (78%)	8 (73%)	0·28 (0·00 - 31·15)	0·597

	Antenatal Risk Factors						Postnatal Risk Factors					
	All Episodes N = 524		Included in Model N = 244				All Episodes N = 521		Included in Model N = 127		OR (95% CI)	P value
Unknown	23 (5%)	7 (10%)										
Infant characteristics												
Gender (male)	284 (63%)	44 (64%)	149 (71%)	23 (66%)	0·72 (0·26 - 1.98)	0·521	284 (63%)	44 (64%)	75 (65%)	9 (82%)	2·66 (0·06 - 119·69)	0·614
WAZ at birth	-0·8 (-1·4, -0·1)	-0·5 (-1·4, -0·1)	-0·8 (-1·5, -0·1)	-0·8 (-1·6, 0·1)	0·96 (0·62 - 1·51)	0·875	0·2 (-0·7, 1·1)	-0·25 (-1·77, 0·73)	0·6 (-0·5, 1·3)	0·2 (0·0, 0·9)	1·12 (0·22 - 5·85)	0·892
Maternal HIV exposure	127 (28%)	17 (25%)	28 (13%)	6 (17%)	1·54 (0·35 - 6·79)	0·568	127 (28%)	17 (25%)	13 (11%)	3 (27%)	308·86 (0·02 - 5853189)	0·254
Age (mid-interval in days)	4·7 (2·9 - 7·1)	2·3 (1·1 - 4·2)	5·2 (2·9 - 7·4)	2·5 (1·5 - 3·4)	0·76 (0·62 - 0·93)	0·006	4·7 (2·9 - 7·1)	2·35 (1·13 - 4·19)	5·2 (3·3 - 7·5)	2·0 (0·7 - 2·8)	0·48 (0·18 - 1·28)	0·142
SES quartiles (compared to high SES)												
Lowest SES	121 (27%)	12 (17%)	58 (28%)	4 (11%)	0·33 (0·07 - 1·59)	0·168	117 (26%)	16 (23%)	43 (37%)	2 (18%)	1·20 (0·01, 100·91)	0·935
Low-mod SES	154 (34%)	24 (35%)	74 (35%)	12 (34%)	1·00 (0·27 - 3·71)	0·994	65 (14%)	15 (22%)	18 (16%)	4 (36%)	6·16 (0·05, 699·62)	0·451
Mod-high SES	94 (21%)	19 (28%)	38 (18%)	10 (29%)	1·35 (0·33 - 5·58)	0·677	81 (18%)	12 (17%)	25 (22%)	3 (27%)	2·45 (0·09, 155·99)	0·672

	Antenatal Risk Factors						Postnatal Risk Factors					
	All Episodes N = 524		Included in Model N = 244				All Episodes N = 521		Included in Model N = 127		OR (95% CI)	P value
High SES	83 (18%)	14 (20%)	39 (19%)	9 (26%)	1		74 (16%)	9 (13%)	30 (26%)	2 (18%)		
Unknown							115 (25%)	17 (25%)				
Method of feeding												
Duration of exclusive breast feeding (months)	2·0 (1·0 - 3·5)	2·1 (1·0 - 3·6)	1·8 (1·0 -3·2)	2·0 (1·0 – 4·0)	1·10 (0·84 - 1·45)	0·470	4·0 (2·4, 9.0)	3·64 (3·00, 9·14)	4·0 (2·0, 9·1)	3·0 (3·0, 8·9)	0·51 (0·13, 2·01)	0·337
Toluene indoor air pollution												
Below ambient standard	263 (58%)	34 (49%)	203 (97%)	29 (83%)	1							
Above ambient standard	9 (2%)	6 (9%)	6 (3%)	6 (17%)	13·21 (1·96 - 89·16)	0·008	22 (5%)	0 (0%)	17 (15%)	0 (0%)	1·00 (0·98, 1·01)	0·514
Unknown	180 (40%)	29 (42%)										

WAZ, weight-for-age z-score; HIV, human immunodeficiency virus; SES, socio-economic status

Supplemental Table 6: Multivariate analysis for lower respiratory tract infection (LRTI) and postnatal environmental exposures

Smoke Exposure (N = 875)		
	IRR (95% CI)	P value
Site		
Mbekweni	1·23 (0·89 - 1·70)	0·207
Smoke exposure		
Maternal self-report smoking	1·22 (0·89 - 1·70)	0·221
Any household member self-report smoking	0·94 (0·68 - 1·30)	0·712
Infant characteristics		
Male	1·67 (1·30 - 2·15)	0.000
WAZ at birth	0·93 (0·83 - 1·04)	0·226
Maternal HIV exposure	1·31 (0·90 - 1·91)	0·160
Age in months	0·90 (0·88 - 0·93)	0·000
SES quartiles		
Lowest SES	1·26 (0·87 - 1·83)	0·218
Low-mod SES	1·63 (1·15 - 2·33)	0·006
Mod-high SES	0·98 (0·68 - 1·43)	0·925
High SES	1	
Method of feeding		
Duration of exclusive breast feeding (months)	0·97 (0·91 - 1·04)	0·361

Indoor Air Pollutant Exposure (N = 429)		
	IRR (95% CI)	P value
Site		
Mbekweni	0·91 (0·61 - 1·37)	0·661
Indoor air pollutant exposure		
PM_{10} above ambient standard	0·61 (0·33 - 1·12)	0·110
Infant characteristics		
Male	1·73 (1·18 - 2·52)	0·005
WAZ at birth	0·94 (0·79 - 1·13)	0·523
Maternal HIV exposure	1·43 (0·76 - 2·70)	0·226
Age in months	0·94 (0·90 - 0·98)	0·002
SES Quartiles		
Lowest SES	1·24 (0·73 - 2·11)	0·427
Low-mod SES	1·35 (0·82 - 2·24)	0·240
Mod-high SES	0·78 (0·45 - 1·36)	0·383
High SES	1	
Method of feeding		
Duration of exclusive breast feeding (months)	0·93 (0·85 - 1·02)	0·108

WAZ, weight-for-age z-score; HIV, human immunodeficiency virus; SES, socio-economic status; PM_{10}, particulate matter

Supplemental Table 7: Multivariable analysis for wheezing and postnatal environmental exposures

Smoke Exposure (N = 875)		
	IRR (95% CI)	P value
Self-reported smoke exposure		
Maternal smoking	1·27 (1·03 - 1·56)	0·024
Any household member smoking	1·55 (1·17 - 2·06)	0·002
Infant characteristics		
Male	1·44 (1·18 - 1·74)	<0·001
WAZ at birth	0·96 (0·88 - 1·04)	0·334
Maternal HIV exposure	0·58 (0·40 - 0·85)	0·006
SES quartiles		
Lowest SES	0·99 (0·73 - 1·35)	0·973
Low-mod SES	1·28 (0·97 - 1·70)	0·079
Mod-high SES	1·52 (1·16 - 1·99)	0·002
Infant feeding		
Duration exclusively breast fed in months	0·98 (0·93 - 1·03)	0·410
Indoor Air Pollutant Exposure (N = 336)		
	IRR (95% CI)	P value
Indoor air pollution		
Toluene above ambient standard	0·60 (0·35 - 1·05)	0·071

Particulate Matter (PM_{10}) above ambient standard	0·84 (0·56 - 1·26)	0·402
Benzene above ambient standard	1·17 (0·87 - 1·57)	0·291
Infant characteristics		
Male	1·45 (1·09 - 1·93)	0·011
WAZ at birth	0·91 (0·80 - 1·04)	0·183
Maternal HIV exposure	0·98 (0·58 - 1·65)	0·934
SES quartiles		
Lowest SES	0·90 (0·57 - 1·42)	0·646
Low-mod SES	1·07 (0·70 - 1·64)	0·758
Mod-high SES	1·78 (1·20 - 2·64)	0·004
Infant feeding		
Duration exclusively breast fed in months	0·89 (0·83 - 0·96)	0·003

WAZ, weight-for-age z-score; HIV, human immunodeficiency virus; SES, socio-economic status

Supplemental Table 8: Multivariate analysis for combined antenatal and postnatal environmental exposures

Wheeze		
	IRR (95% CI)	P value
Combined		
Smoke exposure	1·79 (1·34 - 2·38)	<0·001
Infant characteristics		
Male	1·45 (1·20 - 1·77)	<0·001
WAZ at birth	0·95 (0·87 - 1·04)	0·239
Maternal HIV exposure	0·50 (0·34 - 0·74)	0·001
SES quartiles		
Lowest SES	0·94 (0·70 - 1·28)	0·698
Low-mod SES	1·26 (0·95 - 1·67)	0·106
Mod-high SES	1·50 (1·15 - 1·97)	0·003
Infant feeding		
Duration exclusively breast fed in months	0·98 (0·93 - 1·03)	0·339
Lower respiratory tract infection (LRTI)		
	Odds Ratio (95% CI)	P value
Site		
Mbekweni	1·19 (0·90 - 1·58)	0·222
Combined		
Smoke exposure	1·39 (0·98 - 1·96)	0·067

Infant characteristics		
Male	1·74 (1·34 - 2·26)	<0·001
WAZ at birth	0·94 (0·84 - 1·06)	0·304
Maternal HIV exposure	1·22 (0·83 - 1·80)	0·310
Age of EPI in months	0·90 (0·88 - 0·93)	<0·001
SES quartiles		
Lowest SES	1·20 (0·82 - 1·75)	0·348
Low-mod SES	1·58 (1·10 - 2·26)	0·013
Mod-high SES	0·95 (0·65 - 1·39)	0·796
Infant feeding		
Duration exclusively breast fed in months	0·96 (0·91 - 1·03)	0·341

WAZ, weight-for-age z-score; HIV, human immunodeficiency virus; EPI, extended programme for immunisation; SES, socio-economic status

Supplemental Table 9: Multivariate analysis for combined environmental tobacco smoke (ETS) and indoor air pollution (IAP) exposures

Wheeze		
	IRR (95% CI)	P value
Combined		
IAP / ETS exposure	1·96 (1·32 - 2·92)	0·001
Infant characteristics		
Male	1·42 (1·17 - 1·73)	<0·001
WAZ at birth	0·95 (0·87 - 1·03)	0·234
Maternal HIV exposure	0·51 (0·34 - 0·75)	0·001
SES quartiles		
Lowest SES	0·99 (0·73 - 1·34)	0·955
Low-mod SES	1·26 (0·96 - 1·67)	0·100
Mod-high SES	1·53 (1·17 - 2·00)	0.002
Infant feeding		
Duration exclusively breast fed in months	1·00 (0·93 - 1·03)	0·365
Lower respiratory tract infection (LRTI)		
	Odds Ratio (95% CI)	P value
Site		
Mbekweni	1·11 (0·84 - 1·46)	0·454
Combined		
IAP / ETS exposure	0·99 (0·66 - 1·50)	0·994

Infant characteristics		
Male	1·67 (1·30 - 2·16)	0·000
WAZ at birth	0·90 (0·83 - 1·05)	0·250
Maternal HIV exposure	1·27 (0·87 - 1·87)	0·218
Age of EPI in months	0·90 (0·88 - 0·93)	0·000
SES quartiles		
Lowest SES	1·29 (0·89 - 1·88)	0·185
Low-mod SES	1·64 (1·15 - 2·34)	0·006
Mod-high SES	0·99 (0·68 - 1·45)	0·976
Infant feeding		
Duration exclusively breast fed in months	0·97 (0·91 - 1·03)	0·311

WAZ, weight-for-age z-score; HIV, human immunodeficiency virus; EPI, extended programme for immunisation; SES, socio-economic status

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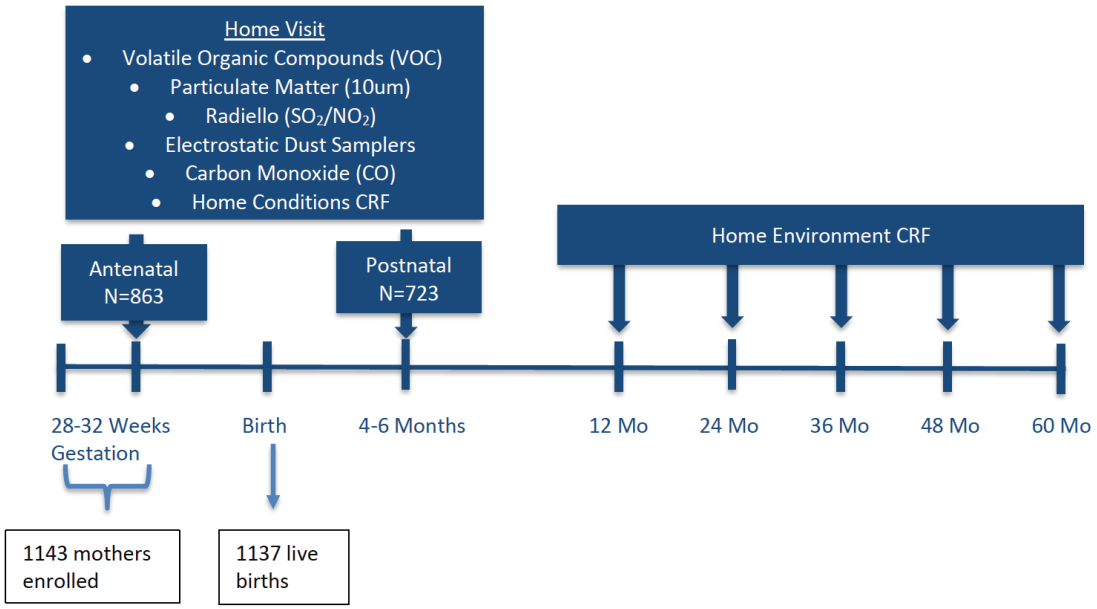
Chapter 7

Summary and recommendations

This study comprises, 1137 mothers enrolled in the Drakenstein Child Health Study (DCHS), with 1143 live births, who were longitudinally followed through the first year of life. The impact of indoor air pollution (IAP) and/or environmental tobacco smoke (ETS) exposure on birth outcomes and on respiratory illness in infants was comprehensively investigated using objective measures of exposures antenatally and postnatally. These included comprehensive measurements of the home environment, and of indoor air pollution exposure in the antenatal and postnatal period, in over 800 homes. (Figure 1) Further, longitudinal quantitative measurements of tobacco smoking and exposure in mothers and infants using urine cotinine were done. The impact of these exposures on child health and lower respiratory tract infections (LRTI) and wheezing in infancy was investigated.

Figure 1: Summary of Home Environment Assessment



1 Summary of results

1.1 Home environment and household exposures

Home visits highlighted the poor living conditions, with one third of homes having 2 or

less pre-defined household dimensions. Despite 92% of homes reporting access to electricity, alternate fuels were still used, particularly in the black African (Mbekweni) community in which 28% of homes used these for cooking and heating. Further, 36% of homes were positioned less than 50m away from road traffic and trucks passing continuously. Using a composite socio-economic score (SES),[1] more than half the participants were in the lowest or low-moderate SES bracket, with the black African population having more people in the lowest SES quartile. Lack of adequate ventilation, poor sanitation and crowding compound the effects of IAP.[2]

Image 1 – Multipurpose single-room dwelling

1.2 IAP exposure

Of the IAP pollutants measured, only benzene (median 5.6ug/m3, IQR 2.6–17.1ug/m3) was significantly above ambient standards.[3] There were significant associations between alternate fuels used for cooking and increased benzene [OR 3.4 (95% CI 2.1–5.4)], carbon monoxide [OR 2.9 (95% CI 1.7–5.0)] or nitrogen dioxide [OR 18.6 (95% CI 3.9–88.9)] levels. IAP levels were higher in winter than in other seasons.

Types of alternate fuels used included paraffin, wood, gas and coal, while other biomass fuels such as animal manure or crop residues were uncommon. These are important findings in the context of societies in transition whereby people are not so poor as to rely on biomass fuels but not sufficiently wealthy to afford available electricity.

1.3 ETS exposure

By using urine cotinine measures, this study reported validated prevalence data on maternal smoking and passive smoke exposure including household tobacco smoke exposure. There were significant differences found in the black African compared to the mixed ancestry communities. Overall, the prevalence of tobacco smoking and ETS exposure was very high. One-third of mothers smoked during pregnancy; significantly higher in the mixed ancestry community with over 50% of mothers smoking. A further 45% of pregnant women were exposed to tobacco smoke. Tobacco smoking in pregnancy is often under-reported and there is limited valid data from LMIC and Africa, especially as self-reports are usually used.[4-6] Also of concern, was that almost 20% infants had birth cotinine measures indicative of “active” smoking, and a further 38% that of passive exposure to tobacco smoke. Over 70% of infants lived in a home with a smoker and in 18% of households there were 3 or more smokers. Also, of note at 6-10 weeks of age infants exposed to more than 3 household smokers had a four-fold increased risk of testing positive for smoke exposure, highlighting that postnatally, environmental ETS exposure was also significant. This study emphasizes that self-reported smoking and exposure under-estimates the true magnitude of ETS exposure and that while maternal smoking prevalence varied between the two communities, exposure from other household members was high. The prevalence of smoking and of passive exposure are substantially higher that those reported from other African regions, where the pooled smoking prevalence in pregnant women was reported as 2.0%, (95%CI 1.2-2.9) the lowest of all LMIC with an overall pooled prevalence of 2.6% (95% CI 1.8-3.6).[4] These are likely to be substantial under-estimates. The findings of this study provide important valid African prevalence data on maternal smoking during pregnancy and ETS exposure to both mothers and infants.

1.4 IAP and ETS exposure: impact on child health

1.4.1. ETS and birth outcomes

Antenatal maternal smoking was associated with decreased infant birth weight-for-age z-score (0.3, 95%CI 0.1–0.5). As birth weight is an important predictor of life-long health outcomes, low birth weight infants are at increased risk for growth, illness or neurodevelopmental problems.[7] Further, low birth weight is a risk factor for LRTI both from respiratory syncytial virus (RSV) and other infectious agents.[8, 9]

1.4.2 IAP or ETS exposure and nasopharyngeal bacterial carriage.

Nasopharyngeal bacterial carriage may be a precursor to the development of LRTI.[10] While it is recognised that ETS exposure impacts on nasopharyngeal bacterial carriage, [11] the impact of IAP exposure on infant nasopharyngeal bacterial carriage has not been well described, particularly in LMIC. In this study, both antenatal and postnatal ETS exposure was associated with *Streptococcus pneumoniae* carriage in mothers and in infants. Other IAP, including carbon monoxide, benzene and nitrogen dioxide also influenced nasopharyngeal bacterial carriage in both mothers and infants. We found that the effect of IAP on carriage was still present even after correcting for other recognised risk factors (weight for age z-score at birth, pre-term, ethnicity, sex, HIV exposure, time on exclusive breastfeeding, average number of people per sleeping room, dwelling category, recent respiratory infection, day care attendance, vaccination, number of other children under 5 years in the household and antibiotic use).[12, 13] Further study of the effect of carriage on the subsequent development of LRTI is planned.

1.4.3 Exposures and lower respiratory tract infection and wheezing

Lower respiratory tract infections (LRTI) were common with 524 episodes of LRTI in the first year of life, incidence 0.49 (95% CI 0.45-0.53) episodes per child year. More episodes of LRTI occurred in the black African infants compared to those of mixed ancestry (61% versus 39%). The wheezing incidence was 0.23 (95% CI 0.21–0.26) episodes per child year. Amongst infants with LRTI, 43% had medically ascertained wheeze, though recurrent wheeze was uncommon (4%).

1.4.3.1. IAP and LRTI

Antenatal particulate matter (PM_{10}) exposure was associated with LRTI (IR 1.43, 95%CI 1.06–1.95) and antenatal toluene (a volatile organic compound) was identified as a novel exposure associated with LRTI-associated hospitalisation (OR 5.13, 95% CI 1.43–18.36) and need for supplemental oxygen (OR 13.21, 95%CI 1.96–89.16). This highlights that alternate cheaper fuels may be associated with severe LRTI and the potential emergence of previously unrecognised compounds impacting on child health.

1.4.3.2 ETS and LRTI

Only antenatal maternal smoking was associated with LRTI in infancy (IR1.62, 95% CI 1.14–2.30).

1.4.3.3 IAP, ETS and wheezing

Both antenatal (IR2.09, 95% CI 1.54–2.84) and postnatal (IR1.27, 95% CI 1.03–1.56) maternal smoking was associated with wheezing, as was antenatal maternal smoke exposure and postnatal household smoke exposure.

1.4.4 Timing of exposures

Antenatal exposures were the predominant risk factor associated with LRTI in the first year of life. This suggests an effect on lung development or immunity, that increases the susceptibility of an infant to developing LRTI. The results highlight the importance of the antenatal period as a key risk time for exposures. Further, there is increasing evidence that lung growth trajectories are set in early life[14, 15] and that adult chronic obstructive respiratory disease risk is set in childhood[16, 17] The consequences of early-life exposures are far reaching with life-long implications including reduced lung function,[18] increased risk of chronic obstructive pulmonary disease, even in non-smokers[19] and genetic and epigenetic changes that may result in generational effects.[20] While a number of studies have compared the effects of antenatal to postnatal ETS exposure on respiratory illnesses,[21-23] there are few studies that have specifically explored the impact of antenatal versus postnatal IAP exposure.[24] The pathophysiologic mechanisms also differ, with antenatal exposures having a direct effect on foetal development and growth through the maternal-foetal circulation [24] and post-natal exposures impacting directly on host

immune defences or directly damaging the lungs. [2]

2 Strengths and limitations

The DCHS provided a unique platform to explore the impact of early-life environmental exposures on child lung health. Strengths of this cohort were the high vaccination rates achieved, timely, free access to care and an effective HIV prevention of mother to child transmission (PMTCT) programme. Prospective data collection, careful LRTI surveillance, longitudinal follow-up, the inclusion of 2 communities with different risk factors and high retention rates were further strengths.

In this study thorough assessment of antenatal and early-life personal exposure to IAP using validated and quantitative measures was done. Successful measurement of IAP in most homes and careful assessment of the home environment further allowed for associations between environmental exposures and LRTI and wheezing to be explored. Each of these associations were tested individually and the associations reported were based on multivariate and multivariable analysis. Urine cotinine measures in mothers and infants provided objective measurement of ETS and served to validate self-reported data on smoking and exposure.

Limitations included the broad definition of LRTI and reliance on care-giver reported accounts of wheezing to characterise respiratory disease. However, the definition of LRTI is consistent with that used in large epidemiological studies and with the WHO revised definitions. Further, large scale epidemiological studies of asthma and wheezing such as International Study of Asthma and Allergies in Childhood (ISAAC) rely on self-reported or parental reported wheeze. In addition, medically ascertained wheeze was also obtained in children who developed LRTI.

A further limitation was that although measures were placed within the homes, the influence of outdoor pollutants could not be excluded. The distinct differences between the two communities in this study who live in close geographical proximity, suggests that exposures may be very population and household specific, however, measured pollutant levels did not differ significantly between the two sites. Further, the very high ETS ex-

posure and the effects associated with this may have led to an underestimation of the effects of IAP.

2.1 Generalisability of results

This community is representative of many peri-urban informal communities and communities living in sub-optimal housing across Southern Africa and in other LMIC settings with a number of environmental factors (air pollution both indoor and outdoor, tobacco smoke, HIV exposure, poor ventilation and crowding) and high incidence of childhood LRTI. However, the notable differences between the black African and mixed ancestry communities within the same area indicates that despite their close physical proximity there is often much inhomogeneity, highlighting the need for any planned intervention to be directed appropriately for the setting.

3 Recommendations

3.1 Future research

This study has identified a number of early life environmental exposures including IAP and ETS that impact on child health in the first year of life. The focus of this study was exposure to indoor air pollution antenatally and in early-life. However, as the child becomes more mobile the external environment, beyond the home, also may be a source of exposures. Evaluating outdoor air pollution and other areas where the child may be exposed to IAP (eg crèche, school) and the combined effect of this with household IAP is required and will provide further insights on the impact of these environmental exposures on child health.

The effect of continued exposure and the impact on recurrent and childhood respiratory illnesses through the childhood years requires longitudinal assessment and follow-up. Retention and longitudinal monitoring of this cohort will also allow for further understanding of the impact of these early life exposures on long term lung health including, growth, development and lung health including lung function.

The impact of IAP on bacterial nasopharyngeal colonisation in both mothers and infants is novel. While an association between environmental exposures and bacterial naso-

pharyngeal carriage was found, further investigation of the impact of carriage on the subsequent development of disease including LRTI and on wheezing illness is required.

Electronic nicotine delivery systems (e-cigarettes), designed to deliver nicotine without tobacco combustion are an emerging threat. Marketed as a safer alternative to conventional cigarettes and as a smoking cessation tool, this poorly regulated industry is gaining popularity amongst young people. Increasing evidence points to nicotine as having significant detrimental effects on lung growth and development as well as being highly addictive.[25] The long-term effects of e-cigarette use are yet to be evaluated and require close monitoring, but given that e-cigarettes contain nicotine the use of these will promote another form of nicotine dependence. Further, evidence suggests that use of e-cigarettes is likely to lead to tobacco smoking in time.[26]

The impact of these exposures on genetic, epigenetic and immunological changes requires further investigation. Studies from high income countries have reported the impact of early-life smoke exposure on the genetic programming that control life-long lung development, aging and susceptibility to obstructive lung diseases[27-29] and on the transgenerational effects of tobacco smoking.[20]

3.2 Interventions and policies

Strategies to reduce household IAP through universal access to affordable electricity or clean fuel must be a primary goal. Where alternate fuel sources are unavoidable, a multi-pronged approach addressing technologies such as improved stoves and combustion design, access to cleaner fuels, improved household ventilation and behaviours that minimise childhood exposure is required.[2]

3.2.1 Regulatory changes

- National housing policies need to ensure IAP exposure is minimised especially when planning and developing new houses.[30] Policies to protect children from adverse exposures and prevent long-term adverse lung health should be standard practice. This may require a multidisciplinary approach with contributions from health, housing and social development sectors to address the socioeconomic issues linked to this

- Ambient air quality standards need to be geographic location specific and acceptable standards require on-going review which may include reducing current standards as health effects may still occur with exposure levels below ambient standards.[31]

- Urgent public health interventions addressing tobacco smoking and household exposure are needed[32] including accessible and effective smoking cessation programmes. A combination of motivational counselling / cognitive behavioural therapy and drug therapies are usually required and currently are the most effective strategy.[33] Such programmes need to be widely available at a primary health care level. In addition, targeted programs aimed at women of child bearing age and pregnant women should be a priority. Smoking cessation and counselling should be incorporated into antenatal programs.

- National policies to regulate and prevent smoking should aim for a tobacco-free society through measures including increased taxation on tobacco products, bans on advertising including marketing tobacco products to youth through sponsored parties and events and enforcing legislation that bans smoking in public places.

Novel approaches to protect children from tobacco smoke may require behavioural changes, air filters, smoking cessation tools and child appropriate aids such as story books. A systematic review and meta-analysis of studies from HIC, found that while these interventions have decreased tobacco smoking pollution in homes, contamination, as measured by air nicotine and PM, still remained. This highlights that despite intensive interventions, exposures in households and personal space are very difficult to control and remain problematic [34].

4 Conclusion

Environmental exposures from IAP and tobacco smoke exposure impact negatively on child health, especially in this LMIC context. The predominant effect of antenatal compared with postnatal exposure on infant LRTI and wheezing suggests an *in utero* developmental lung effect. This study highlights the antenatal period and early life as a critical period for lung development, and identified novel exposures as impacting negatively on child health. This work provides novel South African epidemiological data which is relevant to other LMIC particularly in Africa. Addressing antenatal and early-life environmental exposures is crucial to improving child health. Further longitudinal study of this cohort will provide important information on the long-term respiratory outcomes.

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Appendix A Ethical approval HREC

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences
Faculty of Health Sciences Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
e-mail: sumayah.ariefdien@uct.ac.za
www.health.uct.ac.za/research/humanethics/forms

29 April 2013

HREC REF: 149/2013

Dear Dr A Vanker
c/o Prof H Zar
Paediatrics and Child Health
5th floor, ICH Building
Red Cross War Memorial Children's Hospital

Dear Dr Vanker

PROJECT TITLE: THE IMPACT OF INDOOR AIR POLLUTION AND ENVIRONMENTAL TOBACCO SMOKE EXPOSURE ON CHILDHOOD PNEUMONIA AND CHRONIC LUNG DISEASE.

Thank you for addressing the issues raised by the Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above mentioned study.

Approval is granted for one year till the 15 May 2014.

Please submit a progress form, using the standardised Annual Report Form, if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REC. REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

sAriefdien

This serves to confirm that the University of Cape Town Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

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Appendix A1 DRAKENSTEIN CHILD LUNG HEALTH STUDY

Standard Operating Procedure (SOP)

SOP for Environmental Home Visits

Effective Date:

First Review Date:

Version	Reviewed by/date	Description of changes
1.2	Whitney Barnett	Incorporated CO monitor into procedure
1.3	Whitney Barnett	Linked SOP training with the study training plan

Drafted by: Aneesa Vanker

Author Signature:

Reviewed by: Whitney Barnett **Date:** Jan 2012

Approved by:

PI Signature: **Date of Approval:**

Training Implications

Admin Assistant		Lab Assistant	
Study Nurse Coordinator	X	Lab Manager	
Data Administrator		Medical Officer	X
Data Capturer		Nursing Assistant	
Data Manager		Professional Nurse	
Driver		Project Manager/Coordinator	X
Fieldworker	X	Research Assistant	

TABLE OF CONTENTS:

1 Purpose

The purpose of this SOP is to describe the Home Visits to be performed and the procedures surrounding the devices to be used for measuring indoor air pollution from biomass fuels and tobacco smoke.

2 Background

Two home visits are planned for all participants enrolled on DCLHS. These home visits will occur during the antenatal period following enrolment of the mother. A subsequent home visit will take place within the first 4-6 months of the infant's life.

During these home visits, a questionnaire will be administered by the environmental fieldworker, measurements of the home will be taken and four devices to measure indoor air pollution from Biomass fuels and tobacco smoke will be placed in the home.

3 Scope

This SOP will be used by DCLHS staff involved in performing or assisting with home visits; as delegated by the Project Management Office and indicated by staff job description.

Equipment

1. Questionnaire
2. Laser measuring device
3. Sulphur dioxide (SO2) / Nitrogen dioxide (NO2) passive sampler.
4. Volatile organic compound (VOC) passive sampler
5. Gillian Pump and filter
6. CO Monitor

4 Procedure

a. Pre-arrange a suitable date and time to perform the home visit.
b. Ask permission to visit the home, administer questionnaires and leave devices for measuring indoor air pollution. Explain the purpose of the home visit and what you will be doing while in the home as well as the schedule for picking up devices. Any questions about the home visit should be answered prior to beginning.

c. Identify the main person who will be available to answer questions regarding the home environment.
d. Check each room as per questionnaire and fill in appropriate information before leaving the home. Verify the answers to the question by observing it in the home. (For example, if the answer to how many rooms is 5, the fieldworker should walk around the home and verify that this information is correct).
e. During the antenatal visit, the main living room, the bathroom, the kitchen and mother's bedroom will be measured. Measure each room using laser measure. At the post-natal visit, these living areas will be measured once more as well as the child's room (where the child sleeps). NB: If the main living room/kitchen/ child's room are the same room, field worker only needs to measure once and identify by main purpose of room as well as indicate on the CRF that they were "the same room". (See Home Visit Questionnaire.) Additionally, if the bathroom is external to the home or communal i.e. shared by multiple families, does not need to be measured, fieldworker should note this in the CRF.
f. Find a suitable space in main living room (where majority of people spend majority of time in the home) to leave the 4 devices to measure indoor air pollution.
g. Place the nitrogen dioxide (NO2) / sulphur dioxide (SO2) and volatile organic compound (VOC) passive samplers out of reach of children. These measures should be placed at 1.5 meters height and in the same location, where possible. If not, this should be indicated on the CRF.
h. Explain to household members that these devices will be left in the home for 2 weeks and should not be moved. Record the date and time. (See separate SOP for more details).
i. Place Gillian Pump and the CO monitor in the home in a place high enough to not be in the way. Where possible, it should be placed near the VOC and NO2/ SO2 (radiello) measures; it should be in the same room. Record time and date of leaving device. (see separate SOP for more details)
j. The CO monitor must be turned off between homes. This should be done once inside home and before exiting the home so that measurements are only taken for the interior of a home. The CO monitor must be downloaded at least every 3

days, or more often. When downloading the CO measurements, data for each home should be clearly labeled with PID indicated for first and last reading within each home. This information must be retreived from the CRF at the time of downloading.

k. Retrieval of the Gillian pumps & CO monitor should be done the day after placing them in the home, or as close to 24 hours later as possible. When retrieving the devices, fieldworker must take the CRF with them and fill in the reference numbers as well as the time of pick up before leaving the home.

l. For the dust samplers, two will be placed in the home at both the antenatal visit and then again at the 4-6 month visit (see Dust Sampler SOP for more details). One will be placed in the main living area and one will be placed in the child's room or where the child's room will be after birth. If this is the same space as the main living area, please note this on the Environmental Measures CRF and place only one.

m. Retrieval of the passive devices should be done approximately 2 weeks after placement. When retrieving the devices, fieldworker must take the CRF with them and fill in the reference numbers as well as the time of pick up before leaving the home.

6 Documentation

Home visits will be documented on the completed questionnaires (CRFs). These should be completed at the time of placement and pick up. In addition, tracking forms for all measurement devices sent to the lab should be completed and filed at the respective sites.

7 Training

Training in this SOP will be documented per the DCLH Study Training Plan.

8 Reference

1 WHO, Indoor air pollution and lower respiratory tract infections in children: report of symposium held at the International Society of Environmental Epidemiology, Paris, 4 September 2006. 2007.

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Basic Standard Operating Practice (SOP) for Radiello Measure

Including:

Effective Date:

First Review Date:

Version	Reviewed by/date	Description of changes

Drafted by: Aneesa Vanker

Author Signature:

Reviewed by: **Date:**

Approved by:

PI Signature: **Date of Approval:**

Training Implications

Admin Assistant		Driver	
Clinic Coordinator		Fieldworker	**x**
Clinic Manager		Lab Assistant	
Clinic Nurse		Lab Manager	
Clinician		Medical Officer	**x**
Counsellor		Nursing Assistant	
Data Administrator		Professional Nurse	
Data Capturer		Project Manager	**x**
Data Manager		Research Assistant	**x**

TABLE OF CONTENTS:

Compiled by: Dr Aneesa Vanker

Training Implications:

Table of Contents:

1 Purpose

The purpose of this SOP is to describe the assembly, placement and pick up of the Radiello (in home) measure, which will be used to measuring indoor sulfur dioxide and nitrogen dioxide pollution within the home.

2 Background

During each of the two scheduled home visits, which will take place antenatally and within the first 6 months of the infant's life, the radiello measure will be placed in the home for a period of two weeks.

3 Scope

This SOP will be used by DCLH staff involved in performing or assisting with home visits, in particular the fieldworker who will conduct home visits and place as well as pick up air pollution measures.

4 Equipment

Sulphur dioxide (SO2) / Nitrogen dioxide (NO2) passive sampler (radiello measure).

5 Procedure

The procedure for setting up and dropping off the radiello measure will take place after completion of questionnaire and room measurement.

a. Placement

Find the most appropriate room and space to leave the radiello measure. It is important to consider the following criteria: the device should be placed 1) at breathing level 2) where the majority of persons living in home spend the majority of their time 3) out of the reach of children 4) affixed to stationary object to avoid disturbance 5) where the air is able to flowing over device.

Explain to household members that this device will be left in the home for 2 weeks and should not be moved. Record the date, time and location. (See separate SOP for more details). Leave the information sheet for devices with person who has been answering questions.

Schedule a date/time for pick up of radiello measure, when someone will be at home to allow the fieldworker to collect. This should be two weeks after drop off. Please make a note of the best time for collection on the CRF for environmental measures.

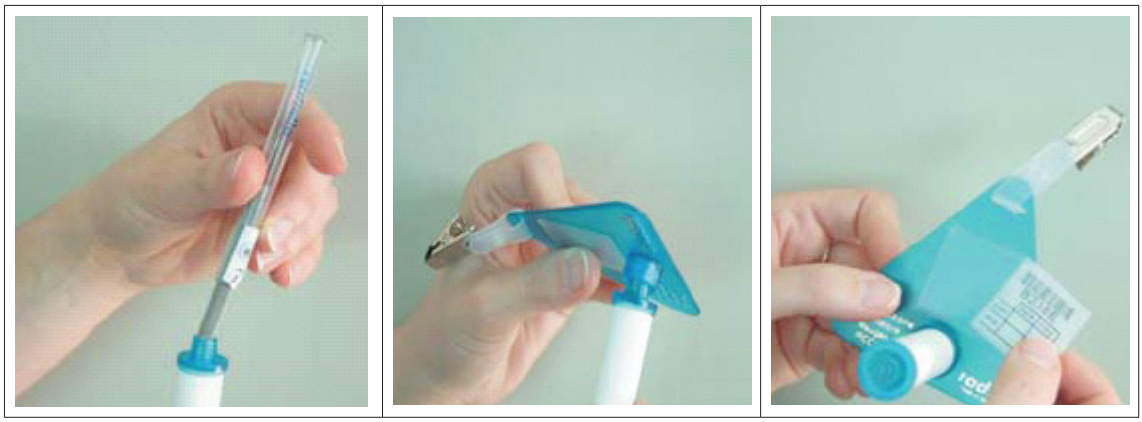
b. Exposing the (SO_2/NO_2) samplE

i. Assemble the supporting plate

- Insert the plastic clip through the slot at the top of the triangular base plate
- Bend the plastic over and clip closed
- Stick the plastic label holder onto the base plate just below the plastic clip

ii. Expose the cartridge & start sampling

- Remove the sample cartridge from its plastic casing
- Open tube
- Get the blue diffusive body ready, being careful not to touch the blue spongy layer (only touch the black plastic components)
- Tip the sample cartridge into the blue diffusive body so that it falls all the way into the holder
- Gently twist blue diffusive body into the blue triangular base plate – make sure this is done upright so that the sample does not fall out of the diffusive body
- No not twist the diffusive body too tightly as this could cause the plastic to break



iii. Label the sample & record sampling data

- Fill in the sample start date and time (hour and minute is necessary) onto the label but do not remove the backing paper
- Record the samples reference number and start date and time on a separate logsheet
- Slide the label into the plastic label holder on the blue triangular base plate
- Close the empty sample cartridge holder (test-tube) and store in a safe place until the sample is ready to be collected.

iv. Clip the sampler in the required location

The final sample should look like this:

C. Collecting the (SO_2/NO_2) sample after 2 weeks of sampling

Once the sample has been exposed for 2 weeks it will need to be collected, labelled and sent to the lab for analysis, following the steps outlined below. Once collected, complete the device measures form regarding pick up details.

i Remove the sampling cartridge

- Unclip the sampler
- Make sure the empty cartridge holder is open and ready for the exposed sample
- Gently unscrew the diffusive body from the triangular base plate whilst keeping the diffusive body upright to prevent the sample from falling out
- Tip the sample cartridge into the original plastic holder and close the lid

ii. Label the sample & record sampling data

- Remove the label from the triangular base plate
- Record the end date and time (in hours and minutes)
- Stick the label onto the plastic cartridge holder
- Make sure all the necessary data is recorded on the sample logsheet (start date & time, end date & time, location & unique reference number)

iii. Sample storage & analysis

- Please store samples in a plastic ziplock bag in a cool place (preferably the fridge) until they are delivered to SGS for analysis

6 Documentation

The device measures form must be initially filled in when leaving the samples in the home and then completed when all the devices have been collected. This information must be completed in real time. This form includes a checklist of where to leave devices, how to set up devices and documentation for drop-off and pick-up.

7 Training

Training in device use to be undertaken by SGS – Aneesa Vanker, Whitney Barnett and Masande Mbovu (fieldworker) and Barnita van Staveld (fieldworker) to be trained. January 2012

- Each Staff member receives or has direct access to the SOP
- Staff members involved in home visits reviews the applicable SOP's on a three monthly basis
- New staff involved in administration of in home environmental measures is trained on

home visit SOP within 14 days of employment.

- Staff members whose duties fall within this SOP scope are retrained within 14 days of the approval of each SOP revision.

APPENDIX A: Radiello Sampler Parts (SO_2/NO_2)

The Radiello samplers consists of 5 parts:

Name	Image	Use
Radiello base plate		A supporting structure for the sample
Radiello base plate clip		Allows the base plate to be hung
Radiello diffusive body		Controls the flow rate over the sample
Radiello sample cartridge		Absorbs pollutants (actual sample which is sent for analysis)
Label		Provides a unique reference number for each sample & for the lab.

General Info and considerations:

- Please be careful not to touch the blue spongy part of the blue diffusive body as this allows air to flow over the sample and any dirt will affect the flow.
- If the diffusive bodies get dirty, please return them to SGS and they can be washed (usually every 3 months)
- Do not touch the sampling cartridge (white tube inside plastic case) as this will affect the sample results

- Please keep exposed samples in their original tubes so they can be sent to the lab for analysis
- Ensure that the unique reference number, start & end dates and times are recorded for each sample
- Please ensure that each sample is labelled on the outside of the plastic tube with the official label before sending it to the lab and that duplicate data is kept on a separate logsheet
- A blank cartridge should be sent with each batch of samples sent for analysis.

APPENDIX B: TRAINING RECORD

THE PERSON WHO SIGNS THIS FORM HAS READ AND UNDERSTOOD THIS SOP

SOP Number: _____

Title: _____

SOP Version: _____

NAME	SIGNATURE	DATE: dd/mm/yy	Comments

APPENDIX A3 Drakenstein Child Lung Health Study (DCLHS)

Basic Standard Operating Practice (SOP) for Volatile Organic Compound Sampler

Including:

Effective Date:

First Review Date:

Version	Reviewed by/date	Description of changes

Drafted by: Aneesa Vanker

Author Signature:

Reviewed by: **Date:**

Approved by:

PI Signature: **Date of Approval:**

Training Implications

Admin Assistant		Driver	
Clinic Coordinator		Fieldworker	**x**
Clinic Manager		Lab Assistant	
Clinic Nurse		Lab Manager	
Clinician		Medical Officer	**x**
Counsellor		Nursing Assistant	
Data Administrator		Professional Nurse	
Data Capturer		Project Manager	**x**
Data Manager		Research Assistant	**x**

TABLE OF CONTENTS:

Compiled by: Dr Aneesa Vanker

1 Purpose

The purpose of this SOP is to describe the assembly, placement and pick up of the VOC sampler, which will be used to measuring indoor organic compounds.

2 Background

During each of the two scheduled home visits, which will take place antenatally and within the first 6 months of the infant's life, the VOC sampler will be placed in the home for a period of two weeks.

3 Scope

This SOP will be used by DCLH staff involved in performing or assisting with home visits, in particular the fieldworker who will conduct home visits and place as well as pick up air pollution measures.

4 Equipment

Volatile organic compound (VOC) passive sampler.

5 Procedure

The procedure for setting up and dropping off the VOC sampler will take place after completion of questionnaire and room measurement.

a. Placement

Find the most appropriate room and space to leave the VOC sampler. It is important to consider the following criteria: the device should be placed 1) at breathing level 2) where the majority of persons living in home spend the majority of their time 3) out of the reach of children 4) affixed to stationary object to avoid disturbance 5) where the air is able to flowing over device.

Explain to household members that this device will be left in the home for 2 weeks and should not be moved. Record the date, time and location. (See separate SOP for more details). Leave the information sheet for devices with person who has been answering questions.

Schedule a date/time for pick up of VOC sampler, when someone will be at home to allow the fieldworker to collect. This should be two weeks after drop off. Please make a note of the best time for collection on the CRF for environmental measures.

b. Exposing the VOC sample

1. Record the sample details including sample reference number, location and start date & time (hours and minutes are necessary).
2. Identify the correct side to open the sample tube. The correct side is the same side as the letter “M” at the start of the reference number (i.e. if you are reading the reference number it will be the left-hand cap assembly).
3. Using one spanner hold the base nut of the cap steady whilst loosening the cap with the second spanner (the cap can be untwisted by hand once it has been loosened).
4. Slide the cap and nut off the sample tube.
5. Press the diffusive cap onto the open end of the sample tube until secure.
6. Clip the sampler into the holder/shelter and ensure it is firmly fixed in place.
7. Store the nut and cap assembly in a safe place until the sample is collected.

c. Collecting the VOC sample after 2 weeks of sampling

Once the sample has been exposed for 2 weeks it will need to be collected and sent to the lab for analysis:

1. Record the sample details including sample reference number, location and end date & time (hours and minutes are necessary). Be sure to check that the tube number is the same as what was recorded initially.
2. Unclip the sampler from the holder/shelter.
3. Remove the diffusive cap from the sample tube.
4. Slide the nut onto the open end of the sample tube and twist on the cap by hand.
5. Tighten the cap using one spanner to hold the base nut of the cap steady

whilst tightening the cap with the second spanner.

6. Please store samples in a plastic ziplock bag in a cool place (preferably the fridge) until they are delivered to SGS for analysis.

6 Documentation

The device measures form must be initially filled in when leaving the samples in the home and then completed when all the devices have been collected. This information must be completed in real time. This form includes a checklist of where to leave devices and documentation for drop-off and pick-up.

7 Training

Training in device use to be undertaken by SGS – Aneesa Vanker, Whitney Barnett and Masande Mbovu (fieldworker) and Barnita van Staveld (fieldworker) to be trained. January 2012

Each Staff member receives or has direct access to the SOP. Staff members involved in home visits reviews the applicable SOP's on a three monthly basis

New staff involved in administration of in home environmental measures is trained on home visit SOP within 14 days of employment.

Staff members whose duties fall within this SOP scope are retrained within 14 days of the approval of each SOP revision.

APPENDIX A: VOC Passives Sampling Procedure

The VOC sampler consists of the following parts:

Name	Image	Use
VOC sampling tube		Absorbs pollutants (actual sample which is sent for analysis) onto a resin-like substance inside the tube.
Sample cap assembly (one on each side) consisting of nut and cap		Seals the sample from ambient air.
Diffusive cap		Prevents large particles of debris or insects from contaminating the sample.

Shelter		Protects the sample from exposure to rain and other elements.
Reference number		Provides a unique reference number for each sampler & for the lab.

General Info and considerations:

- In order to open and close the samples you will need 2 shifting spanners to hold the fixed end-cap assembly nut whilst the cap is loosened/tightened.
- Sample tubes will need to be re-conditioned after each exposure & analysis before they can be re-used. This is done at the lab after analysis but does require some time (i.e. samples cannot be sent back immediately for re-use).
- Individual sample tubes are engraved with a reference number and not each individual sample exposure. This number must be recorded with the start & end dates and times as well as the sample location since the tubes are re-used but the reference number remains the same. Extra caution must be exercised during reporting to ensure that results are not confused.
- Please do not stick any additional labels onto the tubes as this gets stuck during the auto-loading into the lab equipment.
- A blank cartridge should be sent with each batch of samples sent for analysis

APPENDIX B: TRAINING RECORD

THE PERSON WHO SIGNS THIS FORM HAS READ AND UNDERSTOOD THIS SOP

SOP Number: _____

Title: _____

SOP Version: _____

NAME	SIGNATURE	DATE: dd/mm/yy	Comments

INT J TUBERC LUNG DIS 20(6):711

http://dx.doi.org/10.5588/ijtld.16.0260

EDITORIAL

Tobacco smoke exposure in early life: the first African cohort studies

TOBACCO SMOKE (TS) is a leading cause of mortality, responsible for around 6.1 million deaths and for morbidity that causes at least 143.5 million disability-adjusted life years worldwide per year.[1] Maternal smoking is an important risk factor for adverse maternal and foetal outcomes, and environmental TS exposure pre- and post-birth is increasingly recognised to cause childhood illness and developmental delay.[2,3]

In this issue of the *Journal*, the article by Vanker et al. is one of the very few collaborations to report on maternal smoking patterns in a low- to middle-income country.[4] They go further, and have enough reliable data to relate maternal smoking to infant birth outcomes. This setting is all the more relevant as it is becoming a new battleground for tobacco companies who are shifting their emphasis due to taxation and legislation in high-income countries.

The authors are to be congratulated in several ways; although we are not sure of the refusal rate, they provide unique cross-sectional data comparing two well-described local populations of mixed race and predominantly black African communities, suggesting clear differences in smoking prevalence between the two. They are unique in comparing the sensitivity of self-reported versus objective (validated) smoking status using urinary cotinine in both populations. Although relatively expensive compared to exhaled carbon monoxide (especially on this scale), urinary cotinine is a better validation method here as it will not be affected by burning of domestic fossil fuels and, of course, can be collected from newborns without much cooperation! The authors provide rational explanations for the discrepancies in the sensitivity of self-reported versus validated smoking status between the populations, and place them within a live socio-cultural context. The study methodology is strengthened by the fact that all births were recruited from a single hospital so all dyads have identical obstetric services, and, moreover, the ethical element was maintained, as all smokers were offered quit counselling. A member of the study team was present at all 792 births to collect questionnaires and maternal/newborn urine directly. The team maintained a remarkable 91% follow-up rate to repeat the questionnaires and urine testing at 6–10 weeks post-birth; this in itself is no mean feat in any health system, let alone following young women going through chaotic changes in their lives.

One important finding was that high levels of urinary cotinine were more common in infants than their mothers, suggesting high rates of smoking in other household contacts. Environmental TS will be combined in many houses with high levels of pollution from domestic fuels which are increasingly associated with adverse respiratory outcomes, including later COPD.[4] Finally, there was enough complete data to properly correlate maternal smoking status with an adverse birth outcome, which showed the predictable association with decreased infant birthweight for age *Z*-score. The study was large enough with enough follow-up data to allow multi-regression to reduce the effects of confounders.

It is vital that this well-described cohort be followed through early years to adulthood, hopefully with longitudinal lung function and clinical outcomes. I hope the Drakenstein Child Health Study will continue to reveal rich data and contribute to our understanding of public health for low- and middle-income countries as much as landmark cohorts such as the Lung Health Study or Framingham have done for high-income countries. It can supply valuable ammunition for those governments that need it in their battlegrounds.

Professor Keir Lewis
University of Swansea and Hywel Dda University Health Board
Dyfed
United Kingdom
e-mail: k.e.lewis@swansea.ac.uk

Conflicts of interest: none declared.

References

1 GBD Risk Factors Collaborators, Forouzanfar M H, Alexander L, Anderson H R, et al. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015; 386: 2287–2323.
2 Oberg M, Jaakkola M S, Woodward A, Peruga A, Pruss-Ustun A. Worldwide burden of disease from exposure to second-hand smoke: a retrospective analysis of data from 192 countries. Lancet 2011; 377: 139–146.
3 Walker C L, Rudan I, Liu L, et al. Global burden of childhood pneumonia and diarrhoea. Lancet 2013; 381: 1405–1416.
4 Vanker A, Barnett W, Brittain K, et al. Antenatal and early life tobacco smoke exposure in an African birth cohort study. Int J Tuberc Lung Dis 2016; 20: 729–737.
5 Kurmi O P, Semple S, Simkhada P, Smith W C, Ayres J G. COPD and chronic bronchitis risk of indoor air pollution from solid fuel: a systematic review and meta-analysis. Thorax 2010; 65: 221–228.

Appendix B2

Protecting children's lungs by providing clean air during pregnancy?

See Articles page e328

Until a couple of decades ago, air pollution did not feature as a major determinant of ill health among infants. Thus, the words "air", "pollution", and even "smoking" are conspicuously absent from the WHO's 1978 Declaration of Alma-Ata, a major milestone in the field of public health, which expressed "the need for urgent action...to protect and promote the health of all the people of the world".[1] Similarly, the United Nations (UN) Millennium Declaration of 2000 remained silent with regard to clean air.[2] Since then, things have changed and the medical community has become more aware that the health of children greatly depends on breathing clean air. Thus, the 2015 UN resolution that defined the agenda for sustainable development recognises the adverse health effects caused by air pollution, which should be "substantially reduced" by 2030.[3] Air pollution now also features more prominently than before among the risk factors that determine the global burden of disease.[4] In particular, child mortality and morbidity in low-to-middle-income countries has been shown to be strongly associated with household air pollution caused by burning solid fuels (eg, coal, charcoal, wood, dung, and crop residues) for cooking and heating.[5]

In *The Lancet Planetary Health*, Aneesa Vanker and colleagues[7] present findings from the Drakenstein Child Health Study,[6] a birth cohort study in two poor peri-urban communities, some 60 km outside of Cape Town, South Africa. More than 1100 pregnant women were enrolled in this study between 2012 and 2015 to investigate the early-life determinants of illness in an African population. Vanker and colleagues[7] focus on the effect of antenatal and postnatal exposure to indoor air pollution on the occurrence and severity of lower respiratory tract illness (LRTI) or wheezing in children followed up until 1 year of age. A major strength of this unique study,[7] besides its remarkably low loss to follow-up, is the unusually thorough assessment of individual exposure. This assessment included urinary cotinine measurements to estimate active and passive smoking, and more than 4500 antenatal and postnatal home visits, with 24-h air sampling for particulate matter of diameter 10 μm or less (PM_{10}) and carbon monoxide, and 2 weeks' sampling of nitrogen dioxide, sulphur dioxide, and volatile organic compounds.

In brief, the study mainly found increased risks of LRTI (incidence rate ratio 1·62, 95% CI 1·14–2·30; p=0·004) and of wheezing (2·09, 1·54–2·84; p<0·0001) if the mother smoked during pregnancy (depressingly, more than half of the mothers of mixed race smoked during pregnancy). High antenatal indoor exposure to fine dust—ie, PM_{10} levels above 40 μg/m³, the South African standard for ambient air—also increased risk of LRTI (1·43, 1·06–1·95; p=0·008) but not of wheezing. Postnatal exposures were generally less associated with risks of LRTI or wheezing. The possible effect of traffic-related pollution was not reported.

In a subanalysis among children with LRTI, antenatal exposure to toluene above 240 μg/m³ was associated with significantly increased odds of hospitalisation (odds ratio 5·13, 95% CI 1·43–18·36; p=0·012) and requirement for oxygen (13·21, 1·96–89·16; p=0·008). An Australian case-control study[8] found increased risks of asthma in young children with increasing toluene and benzene concentrations in the home, but it is unlikely that, at the observed concentrations, toluene (and similar volatile organic compounds, such as benzene) are causally implicated in the observed respiratory effects. Nevertheless, volatile organic compounds probably represent good markers of combustion-related pollution and they can be measured fairly easily and cheaply by diffusive samplers,[9] as well as in urine.[10] Another promising approach to assess exposure to combustion-related pollution is to measure carbon particles in urine.[11]

Our physical-chemical environment can be envisaged as a series of compartments that are imbricated like matryoshka dolls: the innermost doll is our internal milieu, the next compartment is the personal milieu (micro-environment), the next layers are the indoor environment (meso-environment) and the outdoor environment (macro-environment), and the final layer is the global or planetary environment. Obviously, all compartments communicate with each other. Hence, our internal milieu is polluted by substances absorbed from the external environment (and, sometimes, by

chemicals released from prostheses, dental fillings, or tattoos). Importantly, during pregnancy the mother's internal milieu is also the external milieu of the fetus. Our personal micro-environment might be polluted by active smoking (so-called do-it-yourself air pollution), personal care products and cosmetics, and mobile phones, among other things. The meso-environment concerns the indoor spaces of homes, workplaces, and other buildings or vehicles, in which exposure to numerous types of pollutants can occur: cigarette smoke and other combustion products, substances released from building materials, household chemicals, and specific occupational agents. The outdoor environment is the one that people most often understand as the main environment to be affected by pollutants originating from industry, mining, power generation, agricultural activities, waste processing, urban traffic, among other things. In general, the concentrations of air pollutants are higher in indoor environments, especially if they are poorly ventilated, than in ambient urban air. Moreover, burning solid fuels or biomass causes not only indoor pollution, but also contributes substantially to ambient air pollution;[12] however, this has not been thoroughly quantified for Africa. Conversely, pollutants emitted by industry or traffic also penetrate into homes or schools, depending on building characteristics. Finally, at the planetary level, our environment is influenced by natural phenomena and by human activities that lead to transboundary transport of pollutants and climate changes.

The Drakenstein Child Health Study is undoubtedly a landmark study and its findings are likely to be generalisable to other vulnerable populations, although even poorer and more polluted populations live in rural areas and mega-cities in sub-Saharan Africa. What are the study's implications, so far, in terms of the prevention of LRTI? Vanker and colleagues' rightly advocate effective measures to prevent smoking by women and limiting exposure to indoor air pollution, especially during the antenatal period.[7] Indeed, as shown in their other articles,[13] even excellent medical interventions directed at individuals, such as a high rates of antipneumococcal immunisation and successful prevention of mother-to-child HIV transmission, are unlikely to reduce substantially the incidence of childhood pneumonias in low-to-middle-income countries. Structural interventions leading to decreased poverty and improved air quality are likely to be more effective.

Citizens worldwide are entitled to clean air, just like clean water.[14]

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Appendix B3

Early-life exposures to environmental tobacco smoke and indoor air pollution in the Drakenstein Child Health Study: Impact on child health

Lower respiratory tract infections (LRTIs) are the leading cause of childhood morbidity and mortality in South Africa (SA). Despite sustained efforts to decrease this, including better access to vaccination and strengthening of primary healthcare services, childhood LRTIs continue to impact significantly on child health.[1,2]

SA, a middle-income country, has undergone much social and political change in the past two decades, resulting in urban migration and the mushrooming of peri-urban communities with subsequent health, education and environmental challenges.[3] Despite an increase in electrification, many households continue to rely on alternative fuel sources for cooking and heating.[4] Burning of alternative fuels (such as paraffin, wood, coal and other biomass substances), often in inadequately ventilated homes, contributes to indoor air pollution, a recognised risk factor for respiratory disease.[5] Further, environmental tobacco smoke exposure continues to be problematic despite anti-smoking legislation.[6]

The Drakenstein Child Health Study (DCHS), an SA birth cohort study of 1 000 mother-child pairs, longitudinally investigates the epidemiology, risk factors, aetiology and long-term outcome of childhood diseases, including respiratory illnesses.[7] The study site is in a peri-urban, poor socioeconomic community in the Drakenstein subdistrict, 50 km from Cape Town. Pregnant women were enrolled from two public primary healthcare clinics, Mbekweni (serving a predominantly black African population) and Newman (predominantly mixed-ancestry population), and all deliveries occurred at Paarl Hospital. Children are followed up until at least 5 years of age.

The impact of indoor air pollution (IAP) and environmental tobacco smoke (ETS) exposure on child health was investigated in the DCHS. To measure exposures comprehensively, two home visits, one in the antenatal period (third trimester) and the second postnatally (between 4 and 6 months of the infant's life), were conducted to assess the home environment and to measure the most common indoor air pollutants and byproducts of combustion. Devices placed in participants' homes measured exposure to particulate matter (PM_{10}), carbon monoxide (CO), nitrogen dioxide (NO_2), sulphur dioxide (SO_2) and volatile organic compounds (VOCs).[8] Measurements of IAP were obtained from 863 antenatal and 723 postnatal home visits, providing important SA data on IAP and potential sources of pollution. Measured benzene (VOC) levels were significantly above acceptable SA ambient standards,[9] and together with CO and NO_2, increased levels were associated with fossil fuel use.[8]

Tobacco smoking by pregnant women is often under-reported globally, although household ETS exposure may be high.[10,11] In the DCHS, urine cotinine measures were used to validate maternal self-reported smoking and exposure.[12] Tobacco smoking and exposure was found to be highly prevalent, with a smoking prevalence of >50% in mixed-ancestry mothers. Alarmingly, 18% of infants were born with urine cotinine levels in keeping with active smoking, while a further 30% had levels indicating passive smoke exposure.[12] The impact of the exposures on birth outcomes was significant, with antenatal maternal smoking associated with lower birth weight.[12]

The timing of environmental exposures on the subsequent development of LRTI in infancy has not been well described. Most interestingly, we found that antenatal exposures were the main risk factors associated with LRTI, with maternal smoking in pregnancy or PM_{10} exposure most strongly associated with LRTI. Further, maternal smoking in pregnancy or antenatal passive smoke or PM_{10} exposure was associated with wheezing in infants.[13] Interestingly, toluene, a volatile organic compound, was a novel exposure associated with severe LRTI requiring hospitalisation.[13]

Environmental exposures therefore had a substantial impact on child health and on LRTI. The effect on LRTI of antenatal compared with postnatal exposure suggests an *in utero* developmental lung effect. This study highlights antenatal and early life as a critical period for lung development. Urgent and effective smoking cessation programmes as well as public health interventions focusing on IAP are required. Woman of childbearing age, pregnant women and children in poor communities represent vulnerable populations at risk for long-term health effects of these exposures. Early-life LRTI and environmental exposures have increasingly been associated with the development of chronic obstructive pulmonary disease in adulthood. Further longitudinal study of this cohort will provide important information on the long-term respiratory outcomes.

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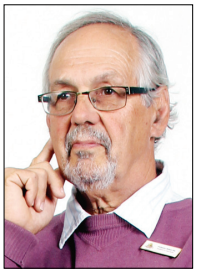

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