Hazelwood
HEALTH STUDY

The Latrobe Early Life Follow-up (ELF) Cohort Study Volume 2

Investigation of possible associations between exposure to mine fire emissions and indicators of lung function measured three years after the fire

July 2018 Version 1.1

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Acknowledgements

The Latrobe Early Life Follow-up (ELF) Study constitutes the child health and development stream of the Hazelwood Health Study. The Latrobe ELF Study forms part of the wider research program of the Hazelwood Health Study and is run by a multidisciplinary group of researchers and administrative staff from the University of Tasmania, Monash University, the University of Melbourne, the University of Sydney and CSIRO. We would like to acknowledge all of these staff for their important contributions.

This study was funded by the Victorian Department of Health and Human Services. The report presents the views of the authors and does not represent the views of the Department.

Most of all, the study team would like to acknowledge the contribution of all families and community members who have participated in the study to date. Specific thanks go to those families who consented to the inclusion of photographs of their children in this Report. Additionally, we would like to acknowledge the Latrobe Community Health Service where the clinical testing was conducted.

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Abbreviations

AX	The area under the reactance curve
BDR	Bronchodilator response
CI	Confidence interval
CSIRO	Commonwealth Scientific and Industrial Organisation
CV	Coefficient of variation
ETS	Environmental tobacco smoke
FOT	Forced oscillation technique
HHS	Hazelwood Health Study
Hz	Hertz (per second)
IQR	Interquartile range
Latrobe ELF Study	Latrobe Early Life Follow-up Study
MICE	Multiple imputation by chained equations
$PM_{2.5}$	Particulate matter with an aerodynamic diameter less than 2.5 micrometres
Rrs	Resistance of the respiratory system
SD	Standard deviation
SEE	Standard error of the estimate
SES	Socio-economic status
Xrs	Reactance of the respiratory system
Z (AX)	Z-score for the area under the reactance curve
Z (Rrs_5)	Z-score for Rrs at a frequency of 5 Hz
Z (Xrs_5)	Z-score for Xrs at a frequency of 5 Hz
ΔAX	Relative change of the area under the reactance curve
ΔRrs_5	Relative change of Rrs at a frequency of 5 Hz
ΔXrs_5	Relative change of reactance at a frequency of 5 Hz

Executive Summary

The Hazelwood open cut coal mine in the Latrobe Valley of Victoria caught fire in February 2014 and burned for nearly six weeks. Several rural towns near the mine were affected by smoke during this period with air quality impacts ranging from minor to severe. The Latrobe Early Life Follow-up (ELF) Study aims to understand the possible influence of exposure to smoke from the fire on the health and development of young children and children born to women who were pregnant at the time. The ELF study has two major streams: an identified cohort study of children from the Latrobe Valley who were recruited during 2015-2016, and a series of anonymous data extraction and data linkage studies.

This Report comprises Volume 2 of a set of reports arising from the Latrobe ELF Cohort Study. Volume 1 described the cohort and the association between mine fire emissions and parent-reported perinatal outcomes. Here we report results of lung function testing of 105 children from the Latrobe ELF Cohort who were exposed to air pollution from the mine fire either prenatally (while *in utero*), or in infancy (aged from birth to 2 years). Investigation of respiratory outcomes in this age group is important, because the early life period is a critical window for lung development and growth. Exposure to harmful factors during this period could potentially increase the risk of long-term adverse respiratory outcomes. The evidence base for the impacts of early life exposure to outdoor air pollution from background sources, such as traffic, on the lung health of children is small but growing. This study is the first that we were aware of to evaluate possible associations between a relatively short, but serious air pollution event in early life and lung function several years after the event.

We estimated smoke exposure for each child in the study by combining information about the hourly spatial distribution of air pollution with information about the daily activity patterns and location of each child during the fire period. Two exposure metrics were calculated.

1. The **average** outdoor concentrations of fine particulate matter with an aerodynamic diameter less than 2.5 micrometres ($PM_{2.5}$). This was the mean of the child's geographically assigned 24 hourly exposures throughout the fire period.
2. The **peak** 24-hour $PM_{2.5}$. This was the highest 24-hour average $PM_{2.5}$ exposure calculated for each child during the mine fire period.

In 2017, three years after the fire, we invited ELF study participants to undertake a lung function test that used sound waves to measure the lungs' resistance to air flow and their stiffness. This non-invasive method is known as the Forced Oscillation Technique (FOT). The FOT is a suitable method for measuring lung function in younger children, because it requires minimal cooperation, and no specific breathing manoeuvres. We also tested if these measures changed after the inhalation of salbutamol, a medication commonly used in the treatment of asthma. The results tell us about lung function on the day of testing. However, it is important to note that we cannot tell if a particular child has or is likely to develop a lung problem based solely on the results of a single round of FOT testing. Three measures were reported from the FOT tests:

1. **Respiratory system resistance (Rrs)**: a measure of how much pressure is required to drive a certain airflow through airways. While this measures the resistance of the respiratory system as a whole, a larger resistance value compared with the reference value commonly indicates airway constriction, airway obstruction or smaller airways.
2. **Respiratory system reactance (Xrs)**: a measure of lung elasticity or stiffness to a pressure wave delivered. While this measures the properties of the respiratory system

as a whole, a larger negative Xrs than the reference value commonly indicates smaller or stiffer lungs.

3. **Area under the reactance curve (AX):** represents the area under the curve of reactance measured at a range of frequencies from 5 Hertz (Hz) to the resonant frequency, which is the point at which Xrs equals zero. While this measures the properties of the respiratory system as a whole, a larger positive AX value than the reference commonly indicates smaller or stiffer lungs.

Given that lung function is associated with age, sex, height and weight, we obtained Z-scores for each parameter after adjustment for these factors. This is a way to standardise the results so that the results from all children, irrespective of their age, sex or height, can be compared. A Z-score of 1 represents a result that is one standard deviation greater than the mean value for children of the same height, weight, age and sex from a standard reference population, while a Z-score of -1 represents a score that is one standard deviation lower than the mean. In addition, we measured the response to inhaled bronchodilator medication by repeating the FOT testing 15 min after inhalation of 200 µg Salbutamol.

Of the 105 children who completed the FOT tests, six were excluded from the analysis due to poor quality of their data. The remaining 99 children had a mean age of four years and one month. Ten were in the *in utero* exposure group, five had mixed pre- and postnatal exposure as they were born during the fire period, and 84 were in the postnatal exposure group. The medians of the average and peak $PM_{2.5}$ exposures during the fire period were 8.0 and 95.6 $\mu g/m^3$, respectively.

Our analysis of the FOT results took into account other factors that are known to affect children's lung function. These were: birthweight, gestational age, environmental tobacco smoke (ETS) exposure, whether their mothers smoked tobacco or drank alcohol during pregnancy, maternal history of asthma, total breastfeeding duration, respiratory medication use in the 24 hours prior to the FOT testing, cold or flu-like illness in the three weeks prior to testing, and indicators of stress and socio-economic status (SES) of their family. Information about some potential risk factors (eg. breastfeeding status) was missing for five participants. We used statistical methods to impute the missing data, so that the results of all participants could be included in the data analysis.

We did not assess the associations between mine fire $PM_{2.5}$ exposure and lung function in the *in utero* and mixed exposure groups separately, because the number of children in these groups was not large enough for statistical analysis.

When all participants were combined (n=99) we did not observe significant associations between coal mine fire $PM_{2.5}$ exposure during infancy and any of the baseline lung function outcome measures. When the 84 children in the postnatal exposure group were evaluated separately, we observed an association between $PM_{2.5}$ and AX, but not with other lung function measures. Each 10 $\mu g/m^3$ increase in average $PM_{2.5}$ exposure was associated with a change in Z-scores for AX of around 24%, in the direction of worsening lung function (risk difference 0.241, 95% confidence interval; CI 0.011 to 0.471, p=0.044). There was also a weak, but not statistically significant, association between a 100 $\mu g/m^3$ increase in peak $PM_{2.5}$ exposure and AX (0.159, 95% CI -0.003 to 0.321, p=0.058) in the direction of poorer lung function.

Separate to the mine fire smoke exposure, we found that maternal smoking during pregnancy was strongly associated with worse lung function. This was indicated by a decreased Xrs (-0.932;

95% CI -1.446 to -0.417, *p*=0.001) and increased AX (0.605; 95% CI 0.054 to 1.155, *p*=0.034) in the whole group. The association was of greater magnitude in the postnatal exposure group alone (Xrs -1.166; 95% CI -1.727 to -0.606, *p*= 0.000; AX 0.743; 95% CI 0.110 to 1.375, *p*=0.024).

Our observations suggest that exposure to smoke from the mine fire could have influenced respiratory system reactance in some children who were exposed to the smoke after their birth. These findings are biologically plausible and the results for mean and peak $PM_{2.5}$ exposure were consistent with each other. However, the statistical associations were close to borderline and the results should be interpreted cautiously. It is also possible that the results occurred by chance or were influenced by known or unknown confounding factors. While we adjusted for the most important factors such as maternal smoking, environmental tobacco smoke and education as a marker of SES, lower educational attainment was unexpectedly found to have a protective association and might not have been the best indicator for socioeconomic status in this group. The measured changes in lung function associated with the fire smoke exposure were small, and in all but the most extreme exposure scenarios, would be unlikely to be of clinical relevance. Furthermore, reductions in lung function as assessed by FOT, and measured on a single occasion, do not necessarily mean that there is a clinical problem or that one might subsequently develop.

In conclusion, we found some evidence for an association between exposure to increased particulate air pollution during the 2014 coal mine fire and small reductions in one of three measures of lung function. It will be important to follow the progress of children in the study to see if the differences we observed change over time. Further study, including testing the comparison group of non-exposed children when they are old enough, will be important for validating these findings.

1. Introduction

The Hazelwood Health Study (HHS) was established to investigate possible health impacts of smoke pollution associated with a fire in the Hazelwood open cut coal mine in the Latrobe Valley of Victoria in 2014. The fire caused elevated concentrations of particulate matter ($PM_{2.5}$) and other air pollutants for several weeks, affecting many nearby communities. The Latrobe Early Life Follow-up (ELF) Study forms one stream of the HHS. It aims to understand the possible influence of the fire smoke on the health and development of children who were aged less than 2 years, or whose mothers were pregnant at the time of the fire. The ELF study has two major streams; (1) an identified cohort study of children from the Latrobe Valley who were recruited during 2015-2016; and (2) a series of anonymised data extraction and data linkage studies. This Report comprises Volume 2 of a set of reports arising from the Latrobe ELF Cohort Study. Volume 1 described the participating cohort and preliminary investigations on the association between mine fire emissions and parent-reported perinatal outcomes. Volume 1 can be found on the Hazelwood Health Study website at www.hazelwoodhealthstudy.org.au/study-findings/study-reports/.

Here we report results of lung function in 105 participants in the Latrobe ELF Cohort who were exposed to air pollution from the mine fire during their early life, either prenatally (i.e. whilst *in utero*), or postnatally during their first two years of life. Investigation of respiratory outcomes in this group is important because the early life period is a critical window for lung development and growth (1). Exposure to harmful factors during this period might increase the risk of long-term adverse respiratory outcomes. The evidence base for the impacts of early life exposure to air pollution and subsequent lung health is small but growing. For example, exposure to traffic-related air pollution during the first year of life has been associated with reduced lung function in both 8-year-old children (2) and in teenage boys (3). In addition, ETS exposure in early life is another globally recognised risk factor for impaired respiratory health in children later in life (4). Maternal tobacco smoking and ETS exposure are associated with many adverse respiratory outcomes including increased risks of respiratory tract infections, wheezing, asthma and reduced lung function in children (5).

Despite increasing evidence suggesting a negative association between prolonged early life air pollution exposure (e.g. annual exposures) and children's respiratory health, studies evaluating short duration of episodic exposures (e.g. wildfires) and later respiratory outcomes are very limited. One study has reported reduced lung function in female adolescent rhesus macaque monkeys after exposure during their infancy to smoke from the Northern California wildfires of 2008 (6). The only human study was a follow up of children who lived through the Great London Smog in 1952. This study found that exposure to the Smog during the first year of life, but not *in utero*, was associated with a 20% increase in the risk of childhood asthma (7). Given the extremely limited evidence about possible effects of exposure to pollution episodes, particularly those of several weeks duration, this study aimed to characterise respiratory impacts in the ELF cohort. The outcomes are intended to guide the relevant departments and policy makers in their work to protect and improve public health.

The study was approved by the Tasmanian Health and Medical Human Research Ethics Committee (reference H14875). Additional approval was received from the Human Research Ethics Committees of Monash University, Monash Health, the University of Melbourne, the University of Sydney and Edith Cowan University.

2. Methods

2.1 Recruitment

All children whose parents completed the ELF baseline survey and consented to further clinical testing (N = 438) were invited to participate in follow up clinics in 2017, three years after the mine fire. All participants were eligible for tests of blood vessel structure and function but only those aged more than three years (n=183) were invited to have lung function tests because these are difficult for very young children. The methods for initial recruitment and data collection for the baseline survey are reported in Volume 1 (8) and are not repeated here. Recruitment for the clinical testing commenced in March 2017 coinciding with the closure of the Hazelwood power station after 52 years of operation.

All invited families were sent an initial approach letter containing a unique log-in to book an appointment online. SMS reminders were used to prompt online bookings. Non-responders were followed up by telephone. Booked participants received a reminder phone call the day before the appointment. Parents/carers were asked to make sure their children had not had a recent infection which may affect the results of lung function testing. Articles in media outlets including newspaper, TV, radio and social media, and a study newsletter promoting the clinical testing which was sent to all enrolled families, aimed to publicise the clinical testing and increase participation.

2.2 Data collection

2.2.1 Data collected during the baseline survey

In the baseline survey, the parent or carer of each child provided information about demographic, family and health characteristics through telephone interview, postal questionnaire or online.. Further details of the baseline survey can be found in our Volume 1 report (8). The survey included residential history, day/night activity during the fire, birthweight, gestational age, breastfeeding, maternal education as a marker of SES, maternal tobacco or alcohol use during pregnancy, maternal stress during pregnancy, parental history of asthma, parental stress during the fire period and the child's exposure to ETS at home. ETS exposure was defined as living in a household with a current smoker.

2.2.2 Additional data collected at the time of lung function testing

On arrival at the clinic, parents or carers of participating children completed a survey to complement the clinical information about their child. The data collected included date and time of the clinic attendance, the child's date of birth, gender, and information about factors which might influence the results of the lung function testing. These included medications used in the past 24 hours plus the presence of any colds or flu-like illnesses in the past three weeks. As socio-economic position can be an important factor for child health, we collected updated information about the child's parent or carers' employment status and the effect of the mine closure on parents' employment and overall stress. In addition, the child's height and weight were recorded using a calibrated stadiometer and portable scales.

2.3 Lung function testing

We measured children's lung function using the Forced Oscillation Technique (FOT) with a TremoFlo C-100 device (Thorasys, Montreal, Quebec, Canada). The FOT is a measure of lung function that is suitable for younger children because it requires minimal cooperation and no specific breathing manoeuvres. While not yet used routinely in clinical practice in Australia, it is used in research settings, especially for younger age groups.

We followed the international recommendations for FOT measurements and calibrated the device every day before use (9, 10). The testing procedure required the children to sit upright on a chair or on the lap of an adult, with their heads in a neutral position and a clip on their noses. The children were then asked to put their lips and teeth around the mouthpiece of the FOT machine, while their cheeks and chin were supported by a staff member. The machine then automatically delivered pressure waves, similar to sound vibrations, while measuring the airway response without the child needing to change how they breathe. Measurements were excluded if artefacts occurred such as mouth or tongue movement, leakage of air, swallowing, talking, glottal closure or having a coherence of < 90% at one or more frequencies of the test waves. At least three acceptable measurements with a coefficient of variation (CV%) of < 10% were required for a valid result to be recorded. This is a typical method used to determine whether measurements are sufficiently similar to each other to demonstrate a consistent way of collecting results (9).

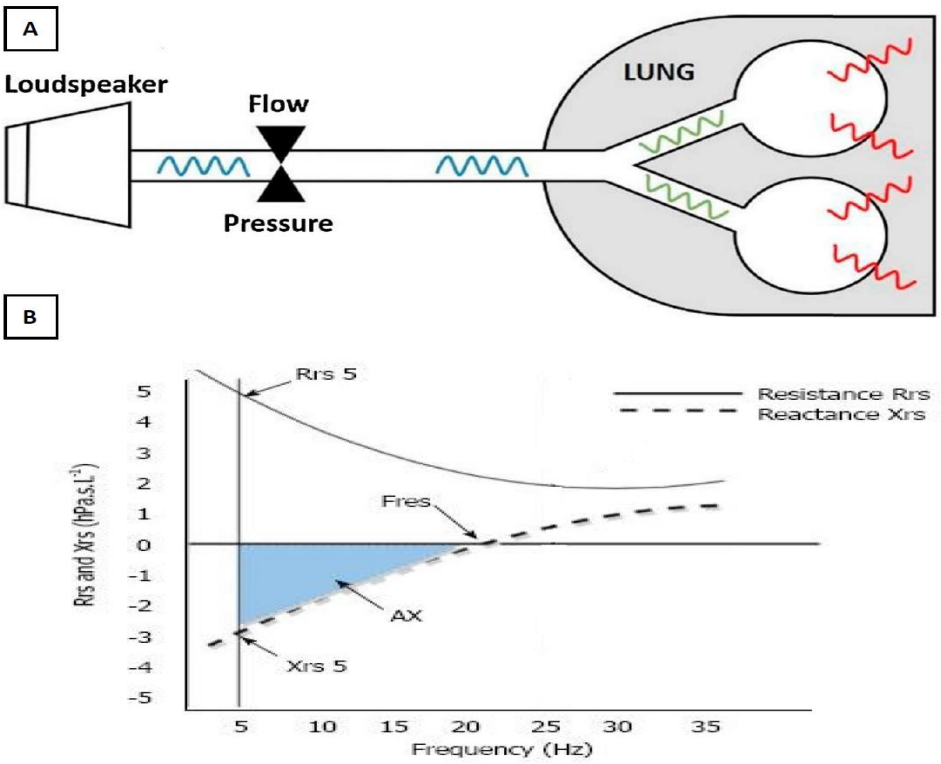


Figure 1. A Schematic presentation of an input oscillometry, and output, for the FOT
A. FOT input oscillometry adapted from Skylogianni et al. (2016). B. FOT output modified from Alblooshi et al. (2017). Rrs 5, resistance at the frequency of 5 Hz; Xrs 5, reactance at the frequency of 5 Hz; AX, the area under the reactance curve; Fres, resonant frequency.

We calculated the mean respiratory system resistance (Rrs) and reactance (Xrs) at a frequency of 5 Hz and the area under the reactance curve (AX) of all acceptable measurements. Rrs measures how much pressure is required to drive a certain airflow through airways, while Xrs measures the stiffness of the respiratory system. AX represents the area under the curve of reactance measurements at a range of frequencies from 5 Hz to the resonant frequency (i.e. the point at which Xrs equals to zero) (Figure 1). A larger Rrs value compared with the reference value can be indicative of airway constriction, airway obstruction, or smaller airways. A larger negative Xrs or a larger positive AX than the reference values is thought to reflect altered peripheral lung mechanics and can be indicative of stiffer or smaller lungs.

Given that lung function is associated with age, gender, height and weight, we obtained Z scores for each parameter from the FOT equipment after adjustment for these factors. This is a way to standardise the results. The Z-scores were calculated according to the equation:

$$Z - \text{score} = (\text{measured value} - \text{reference value})/\text{standard error of the estimate (SEE)}$$ (13).

Increased Z-score for Rrs or AX, and decreased Z-scores for Xrs indicate reduced lung function.

Bronchodilator response

We further tested if these measures changed after the inhalation of bronchodilator (reliever) medication commonly used in the treatment of asthma. The bronchodilator response test is commonly used with spirometry for measuring lung function to assess the reversibility of airflow obstruction (14). In our study, we measured bronchodilator response using FOT to learn more about the lung function of our participants.

We evaluated the bronchodilator response (BDR) by repeating the FOT measurements 15 min after inhalation of 200 µg Salbutamol (Ventolin™, GlaxoSmithKline, Australia) delivered via a disposable spacer (LiteAire, Australia).

Figure 2. Forced oscillation testing in an ELF study volunteer

2.4 Exposure assessment

All children participating in the Latrobe ELF Cohort study fall in to one of four exposure groups:

1. The postnatal exposure group. This group included children who were born between 1 March 2012 and 9 February 2014 and were aged less than two years at the time of the coal mine fire.
2. The *in utero* exposure group. This group comprised children who were born between 1 April and 31 December 2014. The mothers of this group of children had been residing in the Latrobe Valley at the time of the fire when they were pregnant with the child participating in the study.
3. The mixed exposure group. This group comprised a small number of children who were born during the fire period (i.e. between 10 February and 31 March 2014) and were therefore in both the *in utero* and postnatal exposure group.
4. The comparison group. This group consisted of children who were born between 1 January and 31 December 2015 and were conceived after the fire when the associated air pollution had resolved.

All children in the comparison group, and most of the children in the *in utero* exposure group were aged less than three years at the time of testing, and were too young to participate in the lung function tests used in the study. They will be invited to participate in the second round of clinical testing scheduled for 2020, at which time the comparison group will become an age matched comparison group for those tested during 2017.

The children in groups one to three were exposed to the mine fire air pollution across a gradient of severity. Their exposure was influenced by many factors including how close their homes were to the fire, and the amount of time their homes had been in the direct path of the smoke plume from the fire. Their exposure was also determined by the location of their daily activities and if they (or their mother when pregnant), had travelled away from the region during the time of the fire. Information about their day/night time activity patterns during the fire period was collected in the baseline questionnaire.

Our collaborators at the Commonwealth Scientific and Industrial Organisation (CSIRO) Oceans and Atmosphere Flagship implemented meteorological and chemical transport modelling to estimate hourly $PM_{2.5}$ concentrations at a spatial resolution of 1 × 1 km. Further details about the exposure modelling can be found on the Hazelwood Health study website (15). We used these data to calculate 24-hour average exposures for each participant, based on their reported activity patterns and locations each day and night during the fire period defined as 9 February to 31 March 2014.

Two exposure metrics were calculated for each participant.

1. The **average** outdoor concentrations of $PM_{2.5}$ was the mean of the 24 hourly calculated exposures throughout the fire period.
2. The **peak** 24-hour $PM_{2.5}$ was the highest 24-hour average $PM_{2.5}$ exposure calculated for each child during the mine fire period.

2.5 Statistical analysis

We fitted multiple linear regression models to assess the associations between average and peak coal mine fire $PM_{2.5}$ exposures and all lung function measurements. The coefficients from linear regression models represented the changes in Z-scores for every 10 μg/m^3 increase in average $PM_{2.5}$. This is a common increment used in air quality studies and was close to the interquartile range of average $PM_{2.5}$ exposure during the fire period of 8.0 μg/m^3. For peak $PM_{2.5}$ exposure, we report associations per 100 μg/m^3 increase. This corresponded closely to the interquartile range in peak $PM_{2.5}$ exposure of 95.6 μg/m^3.

We evaluated potential confounding factors and effect modifiers selected *a priori* based on the literature as follows: birthweight (continuous variable); gestational age (continuous variable); maternal education as a marker of SES (year 12 or below vs. post-secondary); overall maternal stress during pregnancy (frequently stressed vs. infrequently stressed); and stress during the fire (increased a lot vs. not affected/increased a little); maternal history of asthma (yes vs. no); maternal alcohol use during pregnancy (alcohol vs. no alcohol); maternal tobacco smoking during pregnancy (smoker vs. non-smoker); exposure to ETS in the home (yes or no); duration of breastfeeding (≤ 3 month, vs. > 3 months); any colds or flu-like illnesses in the past three weeks (yes vs. no) and any respiratory medication use 24 hours prior to the FOT testing (yes vs. no).

Five participants had missing values. We used the statistical approach of multiple imputation by chained equations (MICE) to estimate the missing data so that all participants could be included in the analysis. MICE is an acceptable statistical approach to deal with missing values (16). As a sensitivity analysis we also present the results from excluding the participants with imputed data.

The bronchodilator response was calculated as the percent relative change of raw values for Rrs, Xrs and AX from the post-Ventolin measurements compared to the baseline measurements using the equation:

$$\text{Bronchodilator response} = (\text{raw post Ventolin values} - \text{raw baseline values})/|\text{raw baseline values}| \times 100\%$$

As we were using raw values for the bronchodilator response analysis, we further adjusted for sex (male vs. female) and height. Age and weight were excluded because these two variables were highly correlated with height. All statistical analyses were performed using R 3.5.0.

3. Results

3.1 Characteristics of study participants and $PM_{2.5}$ exposure by group

A total of 105 children completed the FOT test, of whom six were excluded due to poor quality of the test. Of the remaining 99 children, ten were in the *in utero* exposure group, five in the mixed exposure group (born during the fire period) and 84 were in the postnatal exposure group.

Table 1 and Table 2 shows the overall and group-specific characteristics of study participants. Girls and boys were nearly equally distributed across the exposure groups, with slightly more girls in the *in utero* and mixed exposure groups. The mothers of most participants did not drink alcohol (88%) or smoke tobacco (82%) during pregnancy, had post-secondary education (63%) and no history of asthma (71%). Nearly one quarter (23%) of children lived in a house with a current smoker and were thus classified as having exposure to environmental tobacco smoke. A third of the children (31%) were breastfed for less than three months. Most mothers were not, or slightly, stressed during pregnancy (88%) or during the fire (61%). More than half (60%) of the children had experienced colds or flu-like illnesses in the past three weeks, and only 11% had used respiratory medication 24 hours before the FOT testing (Table 1). The mean (standard deviation; SD) birthweight and gestational age of all children were 3.4 (0.5) kg and 39.6 (1.9) weeks, respectively. The mean age of all children at the time of FOT testing was 4.1 (0.7) years (Table 2). In addition, the data for a majority of the covariates were complete with the exception of a few where 1-2% were missing; those being maternal alcohol use during pregnancy, breastfeeding duration, birthweight and maternal stress during the fire.

Overall, the median [interquartile range; IQR] of the average $PM_{2.5}$ during the entire 6-week fire period for participants was 8.0 [7.0 – 16.7] $\mu g/m^3$ and the median [IQR] of the peak exposure was 95.6 [62.5 – 158.5] $\mu g/m^3$ (Table 2; Figure 3; Figure 4). Children in the postnatal exposure group (n = 84) were exposed to similar levels of average and peak concentrations of $PM_{2.5}$ compared with the combined group (n = 99) (**Table *2***)

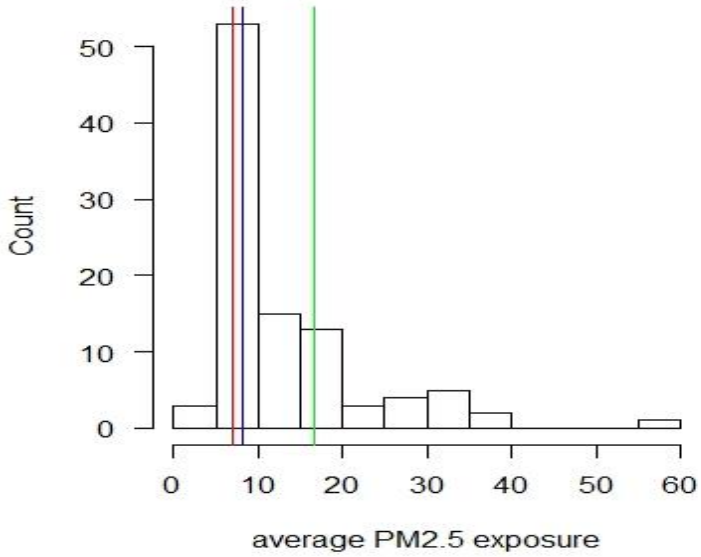


Figure 3. Distribution of average $PM_{2.5}$ (µg/m³) exposure with quartile splits in all participants

The red, blue and green lines represent the first, second and third quartile, respectively.

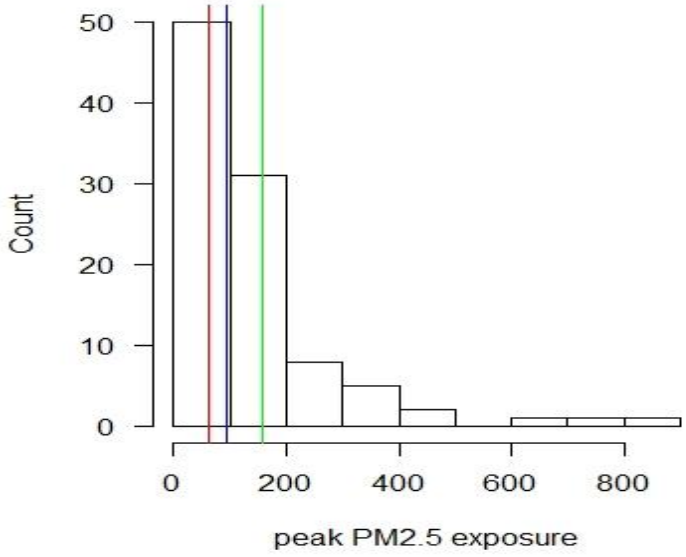


Figure 4. Distribution of peak $PM_{2.5}$ (µg/m³) exposure with quartile splits in all participants

The red, blue and green lines represent the first, second and third quartile, respectively.

Table 1. Characteristics of study participants by exposure groups (categorical variables)

	In utero group	Mixed group	Postnatal group	Overall
	n = 10	n = 5	n = 84	n = 99
		n (%)		
Child's gender				
Female	8 (80)	3 (60)	43 (51)	54 (55)
Male	2 (20)	2 (40)	41 (49)	45 (45)
Missing	0 (0)	0 (0)	0 (0)	0 (0)
Maternal highest education level				
Post-secondary	7 (70)	4 (80)	51 (61)	62 (63)
Year 12 or below	3 (30)	1 (20)	33 (39)	37 (37)
Missing	0 (0)	0 (0)	0 (0)	0 (0)
Maternal alcohol use during pregnancy				
No alcohol	9 (90)	4 (80)	74 (88)	87 (88)
Alcohol	1 (10)	1 (20)	9 (11)	11 (11)
Missing	0 (0)	0 (0)	1 (1)	1 (1)
Maternal smoking during pregnancy				
Non-smoker	7 (70)	5 (100)	69 (82)	81 (82)
Smoker	3 (30)	0 (0)	15 (18)	18 (18)
Missing	0 (0)	0 (0)	0 (0)	0 (0)
Environmental tobacco smoke exposure				
No	7 (70)	5 (100)	64 (76)	76 (77)
Yes	3 (30)	0 (0)	20 (24)	23 (23)
Missing	0 (0)	0 (0)	0 (0)	0 (0)
Maternal history of asthma				
No	5 (50)	3 (60)	62 (74)	70 (71)
Yes	5 (50)	2 (40)	22 (26)	29 (29)
Missing	0 (0)	0 (0)	0 (0)	0 (0)
Breastfeeding duration				
>3 months	6 (60)	5 (100)	56 (67)	67 (68)
<=3 month	4 (40)	0 (0)	27 (32)	31 (31)
Missing	0 (0)	0 (0)	1 (1)	1 (1)
Maternal stress during pregnancy				
Not/sometimes stressed	10 (100)	5 (100)	72 (86)	87 (88)
Frequently stressed	0 (0)	0 (0)	12 (14)	12 (12)
Missing	0 (0)	0 (0)	0 (0)	0 (0)
Effect of coal mine fire on maternal stress				
Not affected/increased a little	6 (60)	2 (40)	52 (62)	60 (61)
Increased a lot	4 (40)	3 (60)	31 (37)	38 (38)
Missing	0 (0)	0 (0)	1 (1)	1 (1)
Cold or flu-like illnesses in the past three weeks				
No	5 (50)	3 (60)	32 (38)	40 (40)
Yes	5 (50)	2 (40)	52 (62)	59 (60)
Missing	0 (0)	0 (0)	0 (0)	0 (0)
Respiratory medication use 24 hours prior to the FOT testing				
No	10 (100)	5 (100)	73 (87)	88 (89)
Yes	0 (0)	0 (0)	11 (13)	11 (11)
Missing	0 (0)	0 (0)	0 (0)	0 (0)

Table 2. Characteristics of study participants by exposure groups (continuous variables)

	In utero group	Mixed group	Postnatal group	Overall
	n = 10	n = 5	n = 84	n = 99
	Mean (SD)			
Birthweight (kg)	3.5 (0.3)	3.5 (0.3)	3.4 (0.6)	3.4 (0.5)
Gestational age (weeks)	40.2 (1.3)	39.6 (2.1)	39.5 (1.9)	39.6 (1.9)
Age at clinic (yrs)	3.0 (0.2)	3.2 (0.1)	4.3 (0.5)	4.1 (0.7)
Height (cm)	95.3 (4.1)	97.5 (1.9)	106.8 (6.2)	105.2 (7.0)
Weight (kg)	15.0 (1.4)	15.9 (1.1)	19.7 (4.9)	19.0 (4.8)
	Median [IQR]			
Average $PM_{2.5}$ ($\mu g/m^3$)	7.6 [7.1 – 8.1]	15.5 [10.0 - 34.4]	7.9 [6.8 – 16.8]	8.0 [7.0 - 16.7]
Peak $PM_{2.5}$ ($\mu g/m^3$)	87.8 [71.3 – 121.2]	158.5 [132.8 – 367.6]	103.4 [60.6 – 150.7]	95.6 [62.5 – 158.5]

3.2 Lung function and bronchodilator response of the study participants

Baseline lung function and BDR results for each group are shown in **Table *3***.

Eight children were excluded from the BDR analysis due to poor quality of their data (n = 2) or a lack of post-bronchodilator measurements (n = 6). Children's lung function was generally improved after inhalation of the bronchodilator, as demonstrated by the decreased Rrs and AX values, and increased Xrs values.

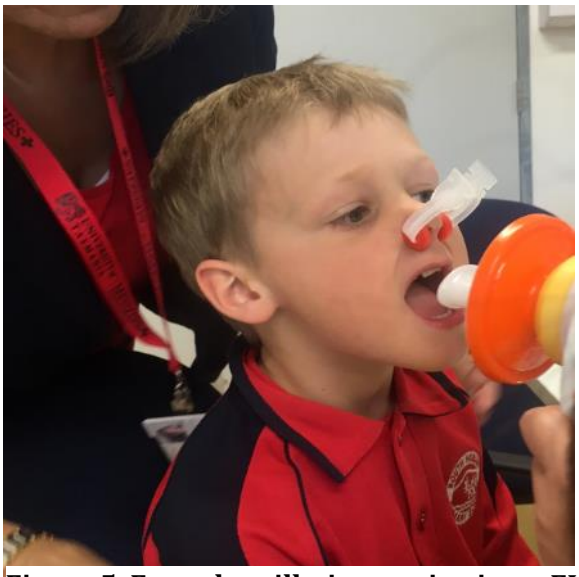


Figure 5. Forced oscillation testing in an ELF study volunteer

Table 3. Baseline lung function and bronchodilator responses in the overall population and by groups

	In utero group	Mixed group	Postnatal group	Overall
	n = 10	n = 5	n = 84	n = 99
			Mean (SD)	
Baseline lung function (Z-score)				
Rrs_5	0.60 (0.63)	0.01 (0.62)	0.56 (0.80)	0.53 (0.78)
Xrs_5	-0.78 (0.79)	-0.35 (0.44)	-0.76 (0.88)	-0.74 (0.85)
AX	0.60 (0.55)	0.29 (0.63)	0.72 (0.92)	0.69 (0.88)
	n = 8	**n = 5**	**n = 78**	**n = 91**
			Mean (SD)	
Bronchodilator response (% baseline measurements)				
ΔRrs_5	-17 (14)	-14 (11)	-19 (11)	-19 (12)
ΔXrs_5	15 (12)	11 (18)	22 (15)	21 (15)
ΔAX	-33 (22)	-34 (23)	-41 (22)	-40 (22)

3.3 Associations between $PM_{2.5}$ exposure, lung function and bronchodilator response

We analysed the association between $PM_{2.5}$ and lung function in all participants (n = 99) and in the postnatal exposure group alone (n = 84). Due to the very small sample size of the *in utero* (n = 10) and mixed (n = 5) exposure groups these were not analysed separately. All models were adjusted for birthweight, gestational age, duration of breastfeeding, maternal education, stress during pregnancy, stress during the fire, history of maternal asthma, alcohol use during pregnancy, ETS exposure, tobacco smoking during pregnancy, any cold or flu-like illnesses in the past three weeks and any respiratory medication use 24 hours prior to the FOT testing.

3.3.1 $PM_{2.5}$ exposure and lung function in all participants

In the full group including children exposed either in utero or postnatally, no associations were observed between average or peak $PM_{2.5}$ and any FOT measurements (***Table 4***)

Maternal tobacco smoking during pregnancy was strongly associated with impaired lung reactance, indicated by a decreased Xrs (-0.932; 95% CI -1.446 to -0.417, p=0.001) and increased AX (0.605; 95% CI 0.054 to 1.155, p=0.034). On the other hand, lower maternal education attainment was unexpectedly associated with higher Xrs (0.463; 95% CI 0.094 to 0.831, p=0.016) and lower AX (-0.409; 95% CI -0.803 to -0.014, p=0.045).

Other covariates including birthweight, gestational age, ETS exposure, maternal stress indicators, maternal alcohol use during pregnancy, maternal asthma, breastfeeding duration, recent cold or flu-like illnesses and respiratory medication use were not associated with any of baseline FOT measurements.

Table 4. Associations between mine fire $PM_{2.5}$ and baseline lung function, all participants

Multivariable analyses*	Z(Rrs_5)		Z(Xrs_5)		Z(AX)	
	Risk difference (95% CI)	***p***	**Risk difference (95% CI)**	***p***	**Risk difference (95% CI)**	***p***
10 µg/m³ increase in average $PM_{2.5}$	0.082 (-0.102 to 0.265)	0.386	-0.116 (-0.303 to 0.071)	0.227	0.183 (-0.017 to 0.382)	0.077
100 µg/m³ increase in peak	0.012 (-0.110 to 0.134)	0.848	-0.040 (-0.164 to 0.084)	0.526	0.077 (-0.057 to 0.210)	0.263

* Average and peak $PM_{2.5}$ were modelled separately. Models adjusted for all *a priori* selected covariates.

3.3.2 $PM_{2.5}$ exposure and lung function in the postnatal exposure group (N=85)

In the postnatal group, each 10 µg/m³ increase in average $PM_{2.5}$ was associated with a 24% increase in Z-scores for AX (0.241; 95% CI 0.011 to 0.471, *p*=0.044). Similarly, for every 100 µg/m³ increase in peak $PM_{2.5}$, we observed a 16% increase in Z-scores for AX (0.159; 95% CI -0.003 to 0.321, *p*=0.058) in the direction of reduced lung function. However, the latter association was on the borderline of statistical significance (***Table 5***)

Table 5. Associations between mine fire $PM_{2.5}$ and children's baseline lung function in the postnatal exposure group

Multivariable analyses*	Z(Rrs_5)		Z(Xrs_5)		Z(AX)	
	Risk difference (95% CI)	***p***	**Risk difference (95% CI)**	***p***	**Risk difference (95% CI)**	***p***
10 µg/m³ increase in average $PM_{2.5}$	0.137 (-0.072 to 0.347)	0.202	-0.179 (-0.383 to 0.025)	0.090	0.241 (0.011 to 0.471)	0.044
100 µg/m³ increase in peak $PM_{2.5}$	0.079 (-0.068 to 0.227)	0.295	-0.088 (-0.233 to 0.056)	0.234	0.159 (-0.003 to 0.321)	0.058

* Average and peak $PM_{2.5}$ were modelled separately. Models included all *a priori* selected covariates.

Sensitivity analysis – participants with complete data only

In the sensitivity analyses restricted to participants who did not have missing data (N= 79), the associations with AX were very similar, although slightly stronger. Each 10 µg/m³ increase in average $PM_{2.5}$ was associated with a 29% increased Z-scores for AX (0.285; 95% CI 0.042 to 0.528, *p*=0.022) and each 100 µg/m³ increase in peak $PM_{2.5}$ was associated with an 18% increase in Z-scores for AX (0.178; 95% CI 0.008 to 0.348, *p*=0.040).

Associations between maternal smoking during pregnancy and reactance were larger in the postnatal group compared with those seen in the whole group (Xrs -1.166; 95% CI -1.727 to -0.606, *p*=0.000; AX 0.743; 95% CI 0.110 to 1.375, *p*=0.024).

Possible interaction between smoking in pregnancy and mine fire smoke exposure

We tested if maternal smoking during pregnancy modified the association between mine fire $PM_{2.5}$ and lung function in this group, but did not find evidence of effect modification (**Table *6***).

Table 6. Tests for effect modification by maternal smoking during pregnancy in the postnatal exposure group

Postnatal exposure group 	*P**		
	Z(Rrs_5)	**Z(Xrs_5)**	**Z(AX)**
Maternal smoking-average $PM_{2.5}$*	0.184	0.233	0.193
Maternal smoking-peak $PM_{2.5}$*	0.296	0.522	0.555

* Average and peak $PM_{2.5}$ were modelled separately. Models included all *a priori* selected covariates.

Possible differences by gender

We conducted a stratified analysis by gender in the postnatal exposure group to assess whether the effects of exposure to coal mine fire emissions differed in girls and boys. While boys tended to have larger sized associations than girls, especially for measures of reactance, the results were not meaningfully different from each other (***Table 7***).

Table 7. Associations between mine fire $PM_{2.5}$ and children's baseline lung function in the postnatal exposure group stratified by gender

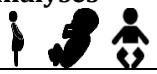
Postnatal group 	Boys		Girls	
	Risk difference* (95% CI)	***P***	**Risk difference* (95% CI)**	***P***
10-unit increase in average $PM_{2.5}$				
Z (Rrs_5)	-0.090 (-0.442 to 0.261)	0.618	0.141 (-0.202 to 0.483)	0.428
Z (Xrs_5)	-0.188 (-0.522 to 0.147)	0.281	-0.051 (-0.377 to 0.276)	0.763
Z (AX)	0.212 (-0.170 to 0.594)	0.287	0.071 (-0.311 to 0.452)	0.719
100-unit increase in peak $PM_{2.5}$				
Z (Rrs_5)	-0.034 (-0.263 to 0.195)	0.773	0.080 (-0.170 to 0.330)	0.535
Z (Xrs_5)	-0.079 (-0.299 to 0.141)	0.488	-0.011 (-0.250 to 0.227)	0.926
Z (AX)	0.181 (-0.064 to 0.425)	0.159	0.035 (-0.243 to 0.313)	0.809

* Average and peak $PM_{2.5}$ were modelled separately. Models included all *a priori* selected covariates.

3.3.3 $PM_{2.5}$ exposure and bronchodilator responses

When the results of all children were analysed together, we did not observe significant associations between a 10 μg/m³ increase in average or a 100 μg/m³ increase in peak $PM_{2.5}$ and changes in Rrs, Xrs or AX following bronchodilator administration (**Table *8***). Similarly, no associations were observed for average or peak $PM_{2.5}$ and bronchodilator responses in the postnatal exposure group alone.

Table 8. Associations between mine fire $PM_{2.5}$ and bronchodilator response

Multivariable analyses* 	ΔRrs_5 (%)		ΔXrs_5 (%)		ΔAX (%)	
	Risk difference (95% CI)	***P***	**Risk difference (95% CI)**	***P***	**Risk difference (95% CI)**	***P***
			All participants			
10-unit increase in average $PM_{2.5}$	0.851 (-1.761 to 3.464)	0.525	-2.487 (-6.173 to 1.199)	0.190	3.728 (-1.683 to 9.139)	0.181
100-unit increase in peak $PM_{2.5}$	0.491 (-1.310 to 2.292)	0.595	-2.161 (-4.685 to 0.362)	0.098	2.669 (-1.059 to 6.396)	0.165
			Postnatal group			
10-unit increase in average $PM_{2.5}$	1.640 (-1.203 to 4.484)	0.263	-2.689 (-6.779 to 1.402)	0.203	5.631 (-0.308 to 11.570)	0.068
100-unit increase in peak $PM_{2.5}$	1.035 (-1.086 to 3.156)	0.343	-1.892 (-4.940 to 1.157)	0.229	3.642 (-0.809 to 8.093)	0.114

* Models adjusted for gender, height and all *a priori* covariates.

4. Discussion

We observed some associations between infant (ie. the first two years following birth) exposure to elevated concentrations of $PM_{2.5}$ during the mine fire and AX, a measure of respiratory system reactance. These results suggest that exposure to mine fire smoke could have influenced lung growth and development in some children, but they are not conclusive. The measured changes in lung function associated with the fire smoke exposure were small, and in all but the most extreme exposure scenarios, would be unlikely to be of clinical relevance. Further, reductions in lung function as assessed by FOT, and measured on a single occasion, do not necessarily mean that there is a clinical problem or that one might subsequently develop.

Results from our sensitivity analyses were very similar to the main findings. The results were marginally stronger when we excluded the five children with missing data. However the results from including all cases, by using imputed data, were likely to be less biased than results from analyses that excluded participants with some missing data (17).

We are not aware of other published studies evaluating early life exposure to smoke from wildfires, or other short duration episodes of air pollution, and lung function in preschool aged children. The only comparable study, in terms of exposure, was conducted in monkeys. The California wildfires of 2008 caused degraded air quality for a period of three weeks in a primate research facility soon after the birth of 50 rhesus macaque monkeys, and their lung function was evaluated in adolescence (6). Unlike our results, these authors found moderate reductions in airway resistance in the exposed animals compared with the unexposed indicating better lung function, although the adverse outcome of increased lung stiffness, a cause of increased reactance, was seen in females.

Epidemiological studies have evaluated the impact of exposure to different concentrations of constant background air pollution, as distinct from short-term pollution episodes, in early life and later lung function. For example, Schultz and colleagues evaluated the association between exposure to traffic-related air pollution during the first year of life and adolescent lung function using a similar approach to ours (18). They reported mixed results with some associations identified between reduced lung function and exposure to oxides of nitrogen but not particulate matter. Studies evaluating exposure to traffic-related $PM_{2.5}$ in infancy and lung function measured with spirometry at 7-10 years of age have reported both reduced (19), or unchanged (20) lung function and no association with bronchodilator response (20). However, these comparisons should be considered with caution because of different populations, metrics, sources and durations of air pollution that were investigated.

Consistent with current literature, we found that maternal tobacco smoking during pregnancy had negative effects on children's lung function. Many epidemiological studies have indicated an adverse effect of maternal tobacco smoking on the lung health of infants (21-23) and children (24-28). Our findings further highlight the need for smoking cessation support for parents, from the pre-conception period and onwards, to improve their children's respiratory health.

The direction of associations between lower maternal education and lung function in our study were unexpected and not consistent with the weight of existing evidence regarding SES and child health (29-32). While we do not have a good explanation for these findings, it could be chance findings in the context of multiple comparisons or inaccurate measurement of maternal education.

This finding should be interpreted cautiously because of the small number of children in the subgroups (e.g. n=37 for children with mothers without post-secondary qualifications).

A strength of the study was our ability to take into account participants' activity patterns to estimate personal $PM_{2.5}$ exposure estimates for each child during the fire period. Further, we were able to use a simple, non-invasive and objective method of evaluating outcomes suitable for young children (33, 34).

However, there are also some limitations that we should acknowledge. First, while we were able to evaluate outcomes in children exposed across a wide range of $PM_{2.5}$, we could not include the group of children with no exposure at all. Children in this group were conceived and born after the fire and were therefore too young to do the FOT testing. We will include these children in our future studies. Second, the exposure estimates were drawn from modelled air quality data because the monitoring conducted during the fire across the Latrobe Valley was incomplete and absent during the first week. Further, our exposure estimates relied upon parental recall of their whereabouts during the mine fire period and there are, therefore, risks of exposure misclassification and recall bias. While most respondents reported that they were very, or extremely, confident of their recall of events during the time of the fire, we were unable to test this objectively. However, there is evidence suggesting a strong correlation between confidence and accuracy of recall in eyewitness studies (35, 36).

It is possible that the results occurred by chance or were influenced by known or unknown confounding factors. We adjusted for the most important factors such as maternal tobacco smoking, ETS exposure and maternal education. Education status is a widely used proxy for social economic status, but in our analysis lower educational attainment was found to have an unexpected protective association and might not have been the best marker of SES in our participants.

It has been shown that improvements in air quality can be associated with improved lung function in children (37, 38). The mine fire episode was brief and air quality in the region was generally very good. It is therefore possible that the differences observed in this study might change as children mature and grow. However, it will be important to continue to monitor lung function in this group, to identify if the differences persist through time. Further research, planned for the year 2020, will include testing the comparison group of non-exposed children. The larger sample size and wider range of exposures in participants at that time will be important for validating these initial findings.

In conclusion, we found some evidence that exposure to greater amounts of particulate air pollution during the mine fire for children in their first two years of life was associated with small reductions in one measure of lung reactance three years after the fire. This suggests that exposure to mine fire smoke could have influenced lung growth and development in some children but the results are not conclusive. It will be important to continue to monitor lung function in this group, to validate these results, and to identify if the differences change through time.

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Document History

Version	Date approved	Approved by	Description
1.0	16 Aug 2018	SPM	Submitted to DHHS
1.1	10 Dec 2018	SPM	Links to Tables 4-8 repaired.