Respiratory Function, Exercise and Ventilation Distribution in Late Adolescence in Survivors Born Extremely Preterm or Extremely Low Birth Weight.

Anne-Marie Gibson

Student Number 342271

Submitted in total fulfilment of the requirements of the degree Doctor of Philosophy - MDHS (Medicine)
December 2013

Royal Children's Hospital

Murdoch Children's Research Institute

Department of Paediatrics, The University of Melbourne

Produced on Archival Quality Paper
1 Abstract

Rationale: Ongoing respiratory morbidity is a common outcome of extremely preterm birth (EP <28 weeks’ gestation) or extremely low birth weight (ELBW; birth weight <1000 g). Respiratory outcomes and exercise capacity in late adolescence for EP/ELBW survivors in the era after surfactant was introduced into clinical practice in the early 1990s have not been reported. Since EP/ELBW survivors have high rates of long-term pulmonary sequelae, including bronchopulmonary dysplasia (BPD), reductions in pulmonary function, exercise capacity and activity levels would be expected compared with normal birth weight (NBW; birth weight >2499 g) controls.

Objective: To compare results from comprehensive lung function and cardiopulmonary exercise testing, including airflow, lung volumes, diffusing capacity and ventilation efficiency at 18 years of age in the largest geographical cohort of EP/ELBW survivors in the post-surfactant era with NBW controls. Within the EP/ELBW group to compare pulmonary outcomes between those who had BPD and those who did not. In the EP only group to determine the relationships between lung function and exercise capacity with growth restriction in utero.

Methods: 208 EP/ELBW survivors (35% had BPD) born in 1991 or 1992, and 153 NBW controls performed spirometry, lung volumes, diffusing capacity, and gas-washout. 114 EP/ELBW subjects (31% had BPD) and 98 NBW controls performed cardiopulmonary exercise tests to a satisfactory level according to standardised guidelines.

Main Results: The EP/ELBW group had significant impairments in spirometry, bronchodilator response, airways resistance, ventilation efficiency in the conducting lung zone, residual volume, and diffusing capacity compared with NBW controls. Those who had bronchopulmonary dysplasia in the newborn period had the greatest impairments. Within the EP only group growth restriction was associated with impairments in airflow and diffusing capacity. Being growth restricted and having BPD did not worsen the airflow impairment. On exercise testing EP/ELBW birth was associated with a significant increase in breathing frequency, and significant reductions in peak ventilation, peak expiratory tidal volume and peak inspiratory tidal volume. EP/ELBW participants with BPD had no further impairments in cardiopulmonary variables related to exercise testing compared with EP/ELBW subjects who did not have BPD. Within the EP only group growth restriction was associated with altered ventilatory patterns and greater use of the ventilatory reserve to achieve maximal exercise.

Conclusions: EP/ELBW survivors have significant impairments in airflow, air-trapping, diffusion and ventilation efficiency within the lungs. These lung function impairments are more severe in those who had BPD as a neonate. EP/ELBW subjects alter their respiration to achieve maximal oxygen consumption levels comparable to NBW controls. BPD is not associated with further cardiopulmonary exercise impairment. Growth restriction was associated with impairment in airflow and gas exchange and diffusion capacity, this was not associated with BPD.
2 Contents

1 Abstract ...................................................................................................................................... 2

3 Declaration ................................................................................................................................. 7

4 Publications related to this thesis .............................................................................................. 8
   4.1.1 Book chapter .............................................................................................................. 8
   4.1.2 Abstracts & Conferences ............................................................................................ 9

4.2 List of Tables..................................................................................................................... 10

4.3 List of Figures .................................................................................................................... 11

4.4 List of Equations ............................................................................................................... 15

4.5 Abbreviations & Definitions ............................................................................................. 16

4.6 Preface.............................................................................................................................. 21

5 Literature review ...................................................................................................................... 22
   5.1.1 Normal respiratory embryology ............................................................................... 22
      5.1.1.1 Asthma ................................................................................................................. 27
      5.1.1.2 Tobacco Smoke..................................................................................................... 27
   5.1.2 Respiratory function changes during infancy and beyond ....................................... 28
      5.1.2.1 Measures of respiratory function and exercise capacity ..................................... 29
         5.1.2.1.1 Spirometry ...................................................................................................... 30
         5.1.2.1.2 Lung volumes ................................................................................................. 37
         5.1.2.1.3 Diffusing capacity of the lungs ....................................................................... 38
         5.1.2.1.4 Ventilation efficiency within the lungs........................................................... 40
         5.1.2.1.5 Muscles of ventilation .................................................................................... 43
         5.1.2.1.6 Cardiopulmonary exercise testing ................................................................. 44
         5.1.2.1.7 Normality and reference equations ............................................................... 48
      5.1.3 Preterm birth ............................................................................................................ 48
      5.1.4 The preterm lung ...................................................................................................... 51
         5.1.4.1 Gestational age versus birth weight..................................................................... 53
         5.1.4.2 Mechanical ventilation ......................................................................................... 54
            5.1.4.2.1 Type of mechanical ventilation .................................................................. 56
         5.1.4.3 Oxygen therapy .................................................................................................... 57
         5.1.4.4 Hyaline membrane disease (HMD) and respiratory distress syndrome (RDS)..... 58
         5.1.4.5 Pulmonary surfactant deficiency ............................................................................ 60
         5.1.4.6 Glucocorticosteroids ............................................................................................ 62
         5.1.4.7 Bronchopulmonary dysplasia – a changing picture ............................................. 63
         5.1.4.8 Other complications of prematurity ................................................................. 70
            5.1.4.8.1 Patent ductus ateriosus (PDA) ................................................................. 70
8.1.2.1 Airflow ................................................................. 129
8.1.2.2 Lung Volumes ...................................................... 132
8.1.2.3 Diffusing capacity ............................................... 134
8.1.2.4 Ventilation efficiency ............................................ 136
8.1.3 Cardiopulmonary exercise .......................................... 138
  8.1.3.1 Metabolic rate .................................................... 138
  8.1.3.2 Cardiovascular function ....................................... 140
  8.1.3.3 Ventilatory function ............................................. 142
  8.1.3.4 Gas exchange .................................................... 145
  8.1.3.5 Metabolic acidosis .............................................. 148
8.1.4 Summary of results EP/ELBW compared with controls ........ 149
8.2 Respiratory function and exercise capacity at 18 years of age in the EP/ELBW survivors, comparing BPD with no BPD ...................................................... 151
  8.2.1 Population characteristics ....................................... 151
  8.2.2 Respiratory function tests ....................................... 152
    8.2.2.1 Airflow .......................................................... 152
    8.2.2.2 Lung volumes .................................................. 155
    8.2.2.3 Diffusing capacity ............................................. 157
    8.2.2.4 Ventilatory efficiency ......................................... 158
  8.2.3 Cardiopulmonary exercise ........................................ 160
    8.2.3.1 Metabolic rate .................................................. 160
    8.2.3.2 Cardiovascular function ...................................... 161
    8.2.3.3 Ventilatory function ........................................... 164
    8.2.3.4 Gas exchange .................................................. 167
    8.2.3.5 Metabolic acidosis ............................................ 170
  8.2.4 Summary of results BPD compared with No-BPD within eth EP/ELBW group ...... 171
8.3 Effects of growth restriction in utero on respiratory function and exercise in EP survivors 173
  8.3.1 Population characteristics of the EP survivors with respiratory function data..... 173
  8.3.2 Respiratory function tests ....................................... 173
    8.3.2.1 Airflow .......................................................... 173
    8.3.2.2 Lung volumes .................................................. 177
    8.3.2.3 Diffusing capacity ............................................. 179
    8.3.2.4 Ventilation efficiency ......................................... 180
  8.3.3 Cardiopulmonary exercise ........................................ 182
    8.3.3.1 Metabolic rate .................................................. 182
    8.3.3.2 Cardiovascular function ...................................... 183
8.3.3.3 Ventilatory function ................................................................. 186
8.3.3.4 Gas exchange ........................................................................ 189
8.3.3.5 Metabolic acidosis .............................................................. 192
8.3.4 Summary of results effects of growth restriction in utero .......... 193

9 Discussion .................................................................................... 194
  9.1 Summary of Main Findings ...................................................... 194
  9.2 Relationships with Other Studies ............................................. 194
  9.3 Strengths of the Study ............................................................. 197
  9.4 Weaknesses of the Study ......................................................... 198
  9.5 Clinical Relevance ................................................................. 199
  9.6 Conclusions and Future Directions ....................................... 201

10 References ................................................................................. 203
11 Appendices ................................................................................ 222
3 Declaration

This is to certify that:

• This thesis comprises only my original work towards the PhD except where indicated in Section 4 (4.1.1 & 4.1.2), “Publications related to this thesis”, page 8,

• Due acknowledgement has been made in the text to all other material used,

• This thesis is fewer than 100 000 words in length, exclusive of tables, maps, bibliographies and appendices.

Signed ......................................................................................

Anne-Marie Gibson
4 Publications related to this thesis

4.1.1 Book chapter
This is rewritten and presented in Chapter 1.4.3
Editor: Peter RIMENSBERGER (Pediatric and Neonatal Intensive Care Unit, University Hospital of Geneva, Switzerland)
Publisher: Springer 2012 ISBN – 13 978 364 201 2181
Textbook: Pediatric and Neonatal Mechanical Ventilation: From Basics to Bedside
Chapter Reference: Part XXVI, Long-term Outcomes after Mechanical Ventilation

1. In neonates
   1.1 Long-term versus short-term effects
   1.2 Effects on respiratory function
   1.3 Neurodevelopmental outcome
   1.4 Effects on neuromuscular function
   1.5 Effects on other aspects of quality of life

Author List: Anne-Marie Gibson,1,2 Doug F Hacking,2,3 Colin R Robertson,1,2,4 Lex W Doyle2,3,4
1 Royal Children’s Hospital, Victoria, Australia; 2 Murdoch Children’s Research Institute, Victoria, Australia; 3 Royal Women’s Hospital, Victoria, Australia, 4 University of Melbourne, Victoria, Australia.
4.1.2 Abstracts & Conferences

- Longitudinal versus cross-sectional lung development in healthy subjects. Author List: Anne-Marie Gibson1,2, Catherine Callanan1,2,3, Colin Robertson1,2,4, Lex Doyle1,2,3; 1Murdoch Children’s Research Institute, Melbourne, VIC 3052; 2University of Melbourne, VIC 3052; 3Royal Women’s Hospital, Melbourne, VIC 3052; 4Royal Children’s Hospital, Melbourne, VIC 3052
  - Accepted as a Thematic Poster to Australia, New Zealand Society for Respiratory Science (ANZSRS) Annual Meeting 2011
  - Awarded Best ANZSRS Poster 2011
  - Accepted as a Thematic Poster at the American Thoracic Society (ATS) annual Meeting 2012

- Normal VO2peak values for Children and Adolescents. Author List: Anne-Marie Gibson1,2, Liam Welsh3; 1Murdoch Children’s Research Institute, Melbourne, VIC 3052; 2Department of Paediatrics, University of Melbourne, VIC 3052; 3Respiratory Medicine Department, Royal Children’s Hospital, Melbourne, VIC 3052
  - Accepted as a Thematic Poster to ANZSRS Annual Meeting 2011

- Lung function abnormalities in EP/ELBW survivors at 18 years compared with NBW control. Author List: A-M Gibson,1,2,3 J Cheong,2,3,4 G Roberts,1 G Opie,5 E Carse,6 C Robertson,1,2 LW Doyle,2,3,4 For the Victorian Infant Collaborative Study (VICS) Group 1Royal Children’s Hospital, 2University of Melbourne, 3Murdoch Childrens Research Institute, 4Royal Women’s Hospital,5Mercy Hospital for Women, 6Monash Medical Centre.
  - Accepted as a Thematic Poster to Thoracic Society of Australia and New Zealand (TSANZ) Annual Meeting 2012
  - Accepted as a Thematic Poster at TSANZ Annual Meeting 2012
  - Accepted as a Thematic Poster at the ATS Annual Meeting 2012

- Maximal exercise abnormalities in EP/ELBW survivors at 18 years of age compared with term NBW control. Author List: A-M Gibson,1,2,3 J Cheong,2,3,4 G Roberts,1 G Opie,5 E Carse,6 C Robertson,1,2 LW Doyle,2,3,4 For the Victorian Infant Collaborative Study (VICS) Group 1Royal Children’s Hospital, 2University of Melbourne, 3Murdoch Childrens Research Institute, 4Royal Women’s Hospital,5Mercy Hospital for Women, 6Monash Medical Centre.
  - Accepted as an Oral Presentation at ANZSRS Annual Meeting 2012
  - Accepted as a Thematic Poster at TSANZ Annual Meeting 2012
  - Accepted as a Thematic Poster at the ATS Annual Meeting 2012
  - Awarded Best Paediatric TSANZ Poster 2012
  - Awarded Best Overall TSANZ Poster 2012
4.2 List of Tables

Table 1: Definition of BPD – Diagnostic criteria ................................................................. 64
Table 2: Evolution of pathology in BPD ([4,77,97,99]) .......................................................... 69
Table 3: Selected cross-sectional respiratory symptoms data from studies of ELBW/preterm survivors, including some with BPD ................................................................. 83
Table 4: Selected cross-sectional lung function data from studies of ELBW/preterm survivors, including some with BPD ........................................................................ 98
Table 5: Selected cross-sectional exercise test data from studies of EP/ELBW birth survivors, including some with BPD ........................................................................... 110
Table 6: Perinatal data comparing the EP/ELBW who were tested at the 18-year follow-up and those who were not .................................................................................. 127
Table 7: Perinatal data comparing the control group who were tested at the 18-year follow-up and those who were not .................................................................................... 128
Table 8: Demographic characteristics of the birth weight groups at the 18 year follow-up ........ 128
Table 9: Multiple regression analysis of the relationship between EP/ELBW and lung function measurements reflecting airflow ........................................................................ 129
Table 10: Multiple regression analysis of the relationship between EP/ELBW and lung function measurements reflecting lung volumes ........................................................................ 132
Table 11: EP/ELBW adjusted regression coefficients – Diffusing capacity ......................... 134
Table 12: EP/ELBW adjusted regression coefficients – Ventilation efficiency ...................... 136
Table 13: Cardiopulmonary EP/ELBW exercise adjusted coefficients ................................. 139
Table 14: Cardiopulmonary EP/ELBW exercise adjusted coefficients ................................. 140
Table 15: Cardiopulmonary EP/ELBW exercise adjusted coefficients ................................. 143
Table 16: Cardiopulmonary EP/ELBW exercise adjusted coefficients ................................. 146
Table 17: Cardiopulmonary EP/ELBW exercise adjusted coefficients ................................. 148
Table 18: Demographic characteristics of the EP/ELBW group comparing those who had and who did not have BPD at the 18 year follow-up ................................................................. 151
Table 19: BPD adjusted regression coefficients in the EP/ELBW group – Airflow ................. 152
Table 20: BPD adjusted regression coefficients in the EP/ELBW group – Lung volumes .......... 155
Table 21: BPD adjusted regression coefficients in the EP/ELBW group – Diffusing capacity .... 157
Table 22: BPD adjusted regression coefficients in the EP/ELBW group – Ventilation efficiency.... 158
Table 23: Cardiopulmonary exercise BPD adjusted regression coefficients in the EP/ELBW group ......................................................................................................................................................... 160
Table 24: Cardiopulmonary exercise BPD adjusted regression coefficients in the EP/ELBW group ......................................................................................................................................................... 162
Table 25: Cardiopulmonary exercise BPD adjusted regression coefficients in the EP/ELBW group ......................................................................................................................................................... 165
Table 26: Cardiopulmonary exercise BPD adjusted regression coefficients in the EP/ELBW group ......................................................................................................................................................... 168
Table 27: Cardiopulmonary exercise BPD adjusted regression coefficients in the EP/ELBW group ......................................................................................................................................................... 170
Table 28: Demographic characteristics of the EP group alone at the 18 year follow-up .......... 173
Table 29: zBW adjusted regression coefficients in the EP group – Airflow ............................. 174
Table 30: zBW adjusted regression coefficients in the EP group – Lung volumes .................... 177
Table 31: zBW adjusted regression coefficients in the EP group – Diffusing capacity ............. 179
Table 32: zBW adjusted regression coefficients in the EP – Ventilation efficiency ................. 180
Table 33: Cardiopulmonary exercise zBW adjusted regression coefficients in the EP group ..... 182
Table 34: Cardiopulmonary exercise zBW adjusted regression coefficients in the EP group ..... 184
4.3 List of Figures

Figure 1: A diagram illustrating the airway structure in the lung and the period in which each develops. (Adapted from (2)) ................................................................. 22
Figure 2: Photomicrograph of lung at 17 weeks’ of gestation showing preacinar branching pattern into the surrounding mesenchyme with pulmonary circulation development. TB, terminal bud; pa, pulmonary artery; pv, pulmonary vein. (Adapted from (2)) ........................................ 23
Figure 3: Photomicrograph of the lung at 23 weeks’ gestation showing capillaries in close contact with alveolar epithelium. (Adapted from (2)) ......................................................... 24
Figure 4: Photomicrograph of the lung at 29 weeks’ gestation showing the mesenchyme decreasing, the blood gas barrier thinning and the appearance of alveoli. TB, terminal bud; sac, saccules (Adapted from(2)) .................................................................................................................. 25
Figure 5: Schematic representing normal lung development and normal decline in lung function compared with abnormal or impaired development that may occur after mechanical ventilation and oxygen therapy, and development of BPD. (Adapted from Tager and colleagues (8)). ........ 26
Figure 6: Spirogram showing volume on the vertical axis and time on the horizontal axis. ................. 31
Figure 7: Spirometry patterns in various pulmonary disorders compared with normal, displayed as volume-time and flow-volume graphics ........................................................................................... 32
Figure 8: Acceptable and unacceptable flow-volume loops and Back-extrapolation. To determine a new time-zero, back-extrapolation is performed using the steepest part of the slope on the volume-time curve, the PEF. This will minimize inaccuracies in FEV₁ due to hesitation at the start of exhalation. (Adapted from (35))........................................................................................................ 34
Figure 9: Evolution of forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) as a function of age. (Adapted from (19)) .............................................................................. 34
Figure 10: Evolution of forced expiratory flow between 25% and 75% of FVC (FEF25-75%) as a function of age. (Adapted from (19)) ............................................................................................... 35
Figure 11: Graphic of a total specific airways resistance (sRₜₒₜ) and effective specific airways resistance (sRₑₑ) loops. Mouth airflow is plotted on the y-axis with inspiratory flows positive and expiratory flows negative. Shift volume is plotted on the x-axis with inspiratory shift volumes positive and those during expiration negative. (Adapted from (39)) ................................................................. 36
Figure 12: Lung volumes as measured by body plethysmography.(45).................................................. 38
Figure 13: A single breath washout curve from the MBW test, illustrating phase I, phase II, phase III and the alveolar phase III slope (red) ................................................................................. 42
Figure 14: Phase III slope analysis illustrating the calculation of Scond and Sacin. ............................... 43
Figure 15: Australian preterm births by gestational age, comparing 1991 and 2009.(74) ................. 50
Figure 16: Australian low birth weight births by birth weight group, comparing 1991 and 2009.(74) ............................................................................................................................................ 50
Figure 17: Hyaline membranes in a neonate with RDS (adapted from (67)) ........................................ 59
Figure 18: Lung histology. (A) Early control lung showing large-sized, simple airspaces, relatively wide septa, and focal early secondary crest formation (asterisks), characteristic of late canalicular/early saccular stage of lung development (infant born at 24 weeks’ gestation; lived for 2 h). (B) Short-term ventilated lung showing widening and increased cellularity of the septa, as well as focal haemorrhages within the air spaces (infant born at 23 weeks; lived for 7 d, ventilated). (C) Late control lung showing complex gas-exchanging parenchyma with abundant
secondary crests (asterisks) and thin alveolar septa, consistent with late saccular/early alveolar stage of lung development (stillborn at 38 weeks). (D) Long-term ventilated lung showing simple, large-sized air spaces with hyper-cellular and thickened septa (infant born at 27 weeks, lived for 12 weeks, ventilated). (22)..................................................................................................................... 66

Figure 19: Patent ductus arteriosus, adapted from (168)..................................................................................................................... 71
Figure 20: Distributional dot plots of zFEV\textsubscript{1}, zFEV\textsubscript{1}/FVC and zFEF\textsubscript{25-75%} at the 18-year follow-up contrasted between the groups. - - - represents ±1.96 SDs from the mean (limits of normal); ... represents the mean value from the reference set; --- represents mean z-score for the group. 130
Figure 21: Distributional dot plots of bronchodilator response (FEV\textsubscript{1} mL), effective airways resistance (sReff) and total airways resistance (sR\textsubscript{tot}) actual values at the 18 year follow-up contrasted between the groups. - - - represents the upper limit of normal (1.30kPa.s\textsuperscript{-1}); --- represents mean value for the group. ..................................................................................................................... 131

Figure 22: Distributional dot plots of zFVC, zTLC, zRV and zVA at the 18 year follow-up contrasted between the groups. - - - represents ±1.96 SDs from the mean (limits of normal); ... represents the mean value from the reference set; -- represents mean z-score for the group. 133
Figure 23: Distributional dot plots of zDLCO and zDLCO/Va at the 18 year follow-up contrasted between the groups. - - - represents ±1.96 SDs from the mean (limits of normal) ... represents the mean value from the reference set; --- represents mean value for the group. ........................................................................ 135
Figure 24: Distributional dot plots of zLCI, SAcin and Scond at the 18 year follow-up contrasted between the groups. - - - represents ±1.96 SDs from the mean (limits of normal) ... represents the mean value from the reference set; --- represents mean value for the group. ........................................................................ 137
Figure 25: Distributional dot plots of maximal work rate actual values at the 18 year follow-up contrasted between the EP/ELBW and control groups. ___ represents mean value for the group. ..................................................................................................................... 139

Figure 26: Distributional dot plots of maximal heart rate values at the 18 year follow-up contrasted between the EP/ELBW and control groups. ___ represents mean value for the group......................................................................... 141
Figure 27: Distributional dot plots of maximal minute ventilation (V'E\textsubscript{max}), breathing frequency (BF), maximal tidal volume (V't\textsuperscript{max}), maximal inspiratory duty cycle (Ti/Ttot) and maximal respiratory reserve (V'E/MVV) actual values at the 18 year follow-up contrasted between the EP/ELBW and control groups. ___ represents mean value for the group. ........................................................................ 144
Figure 28: Distributional dot plots of maximal oxygen consumption (V'O\textsubscript{2}\textsubscript{max}), maximal oxygen consumption per kg (V'O\textsubscript{2}\textsubscript{max}/kg), maximal oxygen saturation (SpO\textsubscript{2}), maximal carbon dioxide production (V'CO\textsubscript{2}\textsubscript{max}), maximal ventilatory equivalent for O\textsubscript{2} (V'E/V'O\textsubscript{2}), maximal ventilatory equivalent for CO\textsubscript{2} (V'E/V'CO\textsubscript{2}) actual values at the 18 year follow-up contrasted between the EP/ELBW and control groups. ___ represents mean value for the group. ........................................................................ 147
Figure 29: Distributional dot plot maximal oxygen consumption at the ventilatory threshold actual values at the 18 year follow-up contrasted between the EP/ELBW and control groups. ___ represents mean V'O\textsubscript{2} at ventilatory threshold for the group. ........................................................................ 148
Figure 30: Distributional dot plots of zFEV\textsubscript{1}, zFEV\textsubscript{1}/FVC and zFEF\textsubscript{25-75%} at the 18-year follow-up in the EP/ELBW groups comparing the group who had BPD to those who did not have BPD as neonates. - - - represents ±1.96 SDs from the mean (limits of normal); --- represents mean z-score for the group. ........................................................................ 153
Figure 31: Distributional dot plots of bronchodilator response (FEV\textsubscript{1} mL), effective airways resistance (sR\textsubscript{eff}) and total airways resistance (sR\textsubscript{tot}) actual values at the 18 year follow-up in the EP/ELBW groups comparing the group who had BPD to those who did not have BPD as neonates. - - - represents the upper limit of normal for sR\textsubscript{eff} and sR\textsubscript{tot} (1.30kPa.s\textsuperscript{-1}); --- represents mean value for the group. ........................................................................ 154
Figure 32: Distributional dot plots of zFVC, zTLC, zRV and zVa calculated at the 18 year follow-up in the EP/ELBW groups comparing the group who had BPD to those who did not have BPD as neonates. - - - represents ±1.96 SDs from the mean (limits of normal); --- represents mean z-score for the group. ................................................................. 156

Figure 33: Distributional dot plot of z-score of DLCO and DLCO/Va at the 18 year follow-up in the EP/ELBW groups comparing the group who had BPD to those who did not have BPD as neonates. - - - represents ±1.96 SDs from the mean (limits of normal) ... represents the mean value from the reference set; --- represents mean z-score for the group. .................................................................................................................................. 157

Figure 34: Distributional dot plot of zLCI, Sacin and Scond at the 18 year follow-up in the EP/ELBW groups comparing the group who had BPD to those who did not have BPD as neonates. - - - represents ±1.96 SDs from the mean (limits of normal) ... represents the mean value from the reference set; --- represents mean value for the group. ........................................................................................................ 159

Figure 35: Distributional dot plots maximal work rate and maximal oxygen consumption adjusted for work rate actual values at the 18 year follow-up in the EP/ELBW groups comparing the group who had BPD to those who did not have BPD as neonates. ___ represents mean value for the group. .............................................................................................................. 161

Figure 36: Distributional dot plots of maximal heart rate, maximal oxygen pulse and stroke volume at the ventilatory threshold actual values at the 18 year follow-up in the EP/ELBW groups comparing the group who had BPD to those who did not have BPD as neonates. ___ represents mean value for the group............................... 163

Figure 37: Distributional dot plots of maximal ventilation rate, maximal breathing frequency, maximal tidal volume, maximal inspiratory duty cycle (Ti/Ttot) and plot ventilatory reserve (V'E/MVV) actual values at the 18-year follow-up in the EP/ELBW groups comparing the group who had BPD to those who did not have BPD as neonates. ___ represents mean value for the group. ......................................................................................................................... 166

Figure 38: Distributional dot plots maximal oxygen consumption, maximal oxygen consumption per kg, maximal carbon dioxide production, maximal ventilatory equivalent for O2 (V'E/V'O2) and maximal SpO2 actual values at the 18 year follow-up in the EP/ELBW groups comparing the group who had BPD to those who did not have BPD as neonates. ___ represents mean values for the group. .............................................................................................................................................. 169

Figure 39: Distributional dot plot maximal oxygen consumption actual values at the 18 year follow-up contrasted between the groups. ___ represents mean V'O2 at ventilatory threshold for the group. .............................................................................................................................................. 170

Figure 40: Distributional dot plot of z-score of zFEV1, zFEV1/FVC and zFFE25-75% at the 18 year follow-up in EP only group. - - - represents -1.96 SDs from the mean (lower limit of normal); ...represents regression line for the model; ...represents the 95% CI. ......................................................... 175

Figure 41: Distributional dot plot of bronchodilator response, sR_eff and sR_tot at the 18 year follow-up in EP only group. - - - represents -1.96 SDs from the mean (lower limit of normal); ...represents regression line for the model, refer to Table 29; ...represents the 95% CI. ......................................................... 176

Figure 42: Distributional dot plot of zFVC, zTLC, zRV and zVa at the 18 year follow-up in EP group. - - - represents -1.96 SDs from the mean (lower limit of normal); ...represents regression line for the model; ...represents the 95% CI. ................................................................. 178

Figure 43: Distributional dot plots of zDLCO and zDLCO/Va at the 18 year follow-up in EP group. - - - represents -1.96 SDs from the mean (lower limit of normal); ...represents regression line for the model; ...represents the 95% CI. ......................................................................................................................... 179

Figure 44: Distributional dot plots of zLCI, Sacin and Scond at the 18 year follow-up in the EP group. - - - represents -1.96 SDs from the mean (lower limit of normal); ...represents regression line for the model; ...represents the 95% CI. ......................................................................................................................... 181
Figure 45: Distributional dot plots of maximal work rate and VO₂/work relationship at the 18 year follow-up in the EP group. ... represents regression line for the model; ... represents the 95% CI. ......................................................................................................................................................... 183

Figure 46: Distributional dot plots maximal heart rate, O₂ pulse and stroke volume at the ventilatory threshold at the 18 year follow-up in the EP group. ... represents regression line for the model; ... represents the 95% CI. .................................................................................................................................................... 185

Figure 47: Distributional dot plot maximal ventilation rate, maximal breathing frequency, maximal tidal volume, maximal inspiratory duty cycle (Ti/Ttot) and ventilatory reserve (V'E/MVV) at the 18 year follow-up in the EP group. ... represents regression line for the model; ... represents the 95% CI. ..................................................................................................................................................... 188

Figure 48: Distributional dot plots maximal O₂ consumption, maximal O₂ consumption per kg, maximal oxygen saturation, maximal CO₂ production, ventilatory equivalent for O₂ and ventilatory equivalent for CO₂ at the 18 year follow-up in the EP group. ... represents regression line for the model; ... represents the 95% CI. .................................................................................................................................................... 191

Figure 49: Distributional dot plot of maximal O₂ consumption at the ventilatory threshold at the 18 year follow-up in the EP group. ... represents regression line for the model; ... represents the 95% CI. ..................................................................................................................................................... 192
4.4 List of Equations

Equation 1: \( \text{PALV} = \text{PPL} - \text{PTP} \) ............................................................................................................ 29
Equation 2: Child A z-score .............................................................................................................. 120
Equation 3: Child B z-score .............................................................................................................. 120
Equation 4: ...................................................................................................................................... 121
Equation 5: ...................................................................................................................................... 121
Equation 6: ...................................................................................................................................... 122
## 4.5 Abbreviations & Definitions

<table>
<thead>
<tr>
<th>Abbreviation/Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>% pred</td>
<td>Percentage of predicted value</td>
</tr>
<tr>
<td>ΔN2/L</td>
<td>Phase III slope, closing volume measured by MBW</td>
</tr>
<tr>
<td>ΔV</td>
<td>Change in volume</td>
</tr>
<tr>
<td>95% CI</td>
<td>Ninety-five percent confidence interval; Confidence interval indicates the reliability of an estimate. A 95% CI reflects a significance level of 0.05.</td>
</tr>
<tr>
<td>AGA</td>
<td>Appropriate for gestational age; within ± 2SD of the mean value from a reference population</td>
</tr>
<tr>
<td>ANZSRS</td>
<td>Australia, New Zealand Society for Respiratory Science <a href="https://www.anzsrs.org.au">www.anzsrs.org.au</a></td>
</tr>
<tr>
<td>AT</td>
<td>Anaerobic threshold</td>
</tr>
<tr>
<td>ATS</td>
<td>American Thoracic Society <a href="https://www.thoracic.org">www.thoracic.org</a></td>
</tr>
<tr>
<td>BAL</td>
<td>Bronchoalveolar lavage</td>
</tr>
<tr>
<td>BDR</td>
<td>Bronchodilator response; change in FEV₁ expressed as either change in millilitres (mL) or change in percent predicted (% pred)</td>
</tr>
<tr>
<td>BF</td>
<td>Breathing frequency (breaths.minute⁻¹, bpm)</td>
</tr>
<tr>
<td>BFmax</td>
<td>Maximal BF</td>
</tr>
<tr>
<td>BPD</td>
<td>Bronchopulmonary dysplasia</td>
</tr>
<tr>
<td>BTPS</td>
<td>Body temperature and pressure, saturated; Lung volume and flow measures are standardised to barometric pressure, body temperature saturated with water at sea level.</td>
</tr>
<tr>
<td>CₐO₂</td>
<td>Arterial O₂ concentration</td>
</tr>
<tr>
<td>CLD₀</td>
<td>Chronic lung disease of infancy</td>
</tr>
<tr>
<td>CMV</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>CO₂</td>
<td>Carbon dioxide</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>CPAP</td>
<td>Continuous positive airway pressure</td>
</tr>
<tr>
<td>CPX</td>
<td>Cardiopulmonary exercise test</td>
</tr>
<tr>
<td>CₕO₂</td>
<td>Venous O₂ concentration</td>
</tr>
<tr>
<td>DL₂CH₂</td>
<td>Diffusion capacity of the lung for acetylene (C₂H₃)</td>
</tr>
<tr>
<td>DLCO</td>
<td>Diffusion capacity of the lung for carbon monoxide (CO) (millilitres per minute per millimetre of Mercury; mL.min.mmHg⁻¹; or expressed as z-scores calculated from a reference set; zDLCO)</td>
</tr>
<tr>
<td>DLCO/Va</td>
<td>Diffusion capacity of the lung for carbon monoxide adjusted for alveolar volume; also referred to as Krogh Coefficient (KCO); (millilitres per minute per millimetre of Mercury per Litre; mL.min.mmHg.L⁻¹; or expressed as z-scores calculated from a reference set; zDLCO/Va)</td>
</tr>
<tr>
<td>DA</td>
<td>Ductus arteriosus</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram, also known as EKG</td>
</tr>
<tr>
<td>ELBW</td>
<td>Extremely low birth weight; birth weight less than 1000 grams</td>
</tr>
<tr>
<td>EMCO</td>
<td>Extracorporeal membrane oxygenation</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>EP</td>
<td>Extremely preterm; infants born less than 28 completed weeks of gestation</td>
</tr>
<tr>
<td>ERS</td>
<td>European Respiratory Society <a href="http://www.ersnet.org">www.ersnet.org</a></td>
</tr>
<tr>
<td>ERV</td>
<td>Expiratory reserve volume (Litres, L)</td>
</tr>
<tr>
<td>FEF&lt;sub&gt;25-75%&lt;/sub&gt;</td>
<td>Forced expiratory flow rate between 25% and 75% of the vital capacity (Litres per second; L.s&lt;sup&gt;-1&lt;/sup&gt;; or expressed as z-scores calculated from a reference set; zFEV&lt;sub&gt;25-75%&lt;/sub&gt;) FEF&lt;sub&gt;25-75%&lt;/sub&gt; is also expressed as MMEF and MEF&lt;sub&gt;25-75%&lt;/sub&gt;</td>
</tr>
<tr>
<td>FEF&lt;sub&gt;x%&lt;/sub&gt;</td>
<td>Forced expiratory flow rate at X% of the vital capacity (Litres per second; L.s&lt;sup&gt;-1&lt;/sup&gt;)</td>
</tr>
<tr>
<td>FETCO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Fractional expired CO&lt;sub&gt;2&lt;/sub&gt; (kilopascals; kPa)</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Forced expiratory volume in the first second (Litres; L; or expressed as z-scores calculated from a reference set; zFEV&lt;sub&gt;1&lt;/sub&gt;)</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;/FVC</td>
<td>Ratio FEV&lt;sub&gt;1&lt;/sub&gt; and FVC (ratio; or expressed as z-scores calculated from a reference set; zFEV&lt;sub&gt;1&lt;/sub&gt;/FVC)</td>
</tr>
<tr>
<td>FiO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Fractional inspired oxygen content</td>
</tr>
<tr>
<td>FOT</td>
<td>Forced Oscillation Technique</td>
</tr>
<tr>
<td>FRC</td>
<td>Functional residual capacity (Litres; L; or expressed as z-scores calculated from a reference set; zFRC)</td>
</tr>
<tr>
<td>FRC&lt;sub&gt;N2&lt;/sub&gt;</td>
<td>FRC measured by MBW, in this case using N&lt;sub&gt;2&lt;/sub&gt; as the inert washout gas</td>
</tr>
<tr>
<td>FRC&lt;sub&gt;pleth&lt;/sub&gt;</td>
<td>FRC measured by body plethysmography, also known as TGV or iTGV</td>
</tr>
<tr>
<td>FRC&lt;sub&gt;SF6&lt;/sub&gt;</td>
<td>FRC measured by MBW, in this case using SF&lt;sub&gt;6&lt;/sub&gt; as the inert washout gas</td>
</tr>
<tr>
<td>f&lt;sub&gt;res&lt;/sub&gt;</td>
<td>Resonant frequency, measured by FOT</td>
</tr>
<tr>
<td>FVC</td>
<td>Forced vital capacity (Litres; L; or expressed as z-scores calculated from a reference set; zFVC)</td>
</tr>
<tr>
<td>GA</td>
<td>Gestational age; number of completed weeks of pregnancy</td>
</tr>
<tr>
<td>G&lt;sub&gt;aw&lt;/sub&gt;</td>
<td>Airways compliance</td>
</tr>
<tr>
<td>Grams</td>
<td>Weight measure (g)</td>
</tr>
<tr>
<td>H&lt;sup&gt;+&lt;/sup&gt;</td>
<td>Hydrogen ions</td>
</tr>
<tr>
<td>Hb</td>
<td>Haemoglobin (grams per Litre; g.L&lt;sup&gt;-1&lt;/sup&gt;)</td>
</tr>
<tr>
<td>HFOV</td>
<td>High frequency oscillatory ventilation</td>
</tr>
<tr>
<td>HMD</td>
<td>Hyaline membrane disease</td>
</tr>
<tr>
<td>HR</td>
<td>Heart rate (beats per minute; bpm)</td>
</tr>
<tr>
<td>HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Maximal HR</td>
</tr>
<tr>
<td>IC</td>
<td>Inspiratory capacity (Litres; L)</td>
</tr>
<tr>
<td>IPPV</td>
<td>Intermittent positive pressure ventilation</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>IRV</td>
<td>Inspiratory reserve volume (Litres; L)</td>
</tr>
<tr>
<td>IUGR</td>
<td>Intra uterine growth restriction, reduced birth adjusted for gestational age</td>
</tr>
<tr>
<td>IVH</td>
<td>Intraventricular haemorrhage</td>
</tr>
<tr>
<td>LBW</td>
<td>Low birth weight; birth weight less than 2500 grams</td>
</tr>
<tr>
<td>LCI</td>
<td>Lung clearance index; a measure of ventilation efficiency within the lungs as measured by inert gas inhalation/exhalation techniques (no units; or expressed as z-scores calculated from a reference set; zLCI)</td>
</tr>
<tr>
<td>M&lt;sub&gt;1&lt;/sub&gt;/M&lt;sub&gt;0&lt;/sub&gt;</td>
<td>First moment ratio, measured by MBW</td>
</tr>
<tr>
<td>M&lt;sub&gt;2&lt;/sub&gt;/M&lt;sub&gt;0&lt;/sub&gt;</td>
<td>Second moment ratio, measured by MBW</td>
</tr>
<tr>
<td>MBW</td>
<td>Multiple breath inert gas washout; measures LCI. Scond and Sacin</td>
</tr>
<tr>
<td>MVV</td>
<td>Maximal voluntary ventilation; V'E/MVV maximal ventilation as a proportion of maximal voluntary ventilation is equivalent to respiratory...</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>--------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>N₂</td>
<td>Nitrogen</td>
</tr>
<tr>
<td>NBW</td>
<td>Normal birth weight; birth weight greater than or equal to 2500 grams</td>
</tr>
<tr>
<td>NEC</td>
<td>Necrotising enterocolitis</td>
</tr>
<tr>
<td>NICHD</td>
<td>National Institutes of Child Health and Human Development</td>
</tr>
<tr>
<td>NO</td>
<td>Nitric oxide</td>
</tr>
<tr>
<td>O₂</td>
<td>Oxygen</td>
</tr>
<tr>
<td>O₂ pulse</td>
<td>Oxygen pulse, oxygen delivered per heart beat (millilitres per beat, mL.beat⁻¹)</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PAH</td>
<td>Pulmonary arterial hypertension</td>
</tr>
<tr>
<td>PALV</td>
<td>Alveolar pressure</td>
</tr>
<tr>
<td>PCO₂</td>
<td>Partial pressure of Carbon dioxide</td>
</tr>
<tr>
<td>PDA</td>
<td>Patent ductus ateriosus</td>
</tr>
<tr>
<td>PEF</td>
<td>Peak expiratory flow (Litres per second; L.s⁻¹)</td>
</tr>
<tr>
<td>PMA</td>
<td>Post menstrual age</td>
</tr>
<tr>
<td>PO₂</td>
<td>Partial pressure of Oxygen</td>
</tr>
<tr>
<td>PPL</td>
<td>Pleural pressure</td>
</tr>
<tr>
<td>PREM</td>
<td>Premature infant</td>
</tr>
<tr>
<td>Preterm</td>
<td>Infants born less than 37 completed weeks of gestation</td>
</tr>
<tr>
<td>PTC</td>
<td>Preterm control</td>
</tr>
<tr>
<td>PTP</td>
<td>Trans-pulmonary pressure</td>
</tr>
<tr>
<td>p-value</td>
<td>Level of significance less than 0.05</td>
</tr>
<tr>
<td>PVL</td>
<td>Periventricular leukomalacia</td>
</tr>
<tr>
<td>Rₕaw</td>
<td>Airways resistance</td>
</tr>
<tr>
<td>RDS</td>
<td>Respiratory distress syndrome</td>
</tr>
<tr>
<td>RER</td>
<td>Respiratory exchange ratio (V'O₂/V'CO₂)</td>
</tr>
<tr>
<td>Rint</td>
<td>Resistance interrupter technique; measure airways resistance</td>
</tr>
<tr>
<td>ROP</td>
<td>Retinopathy of prematurity</td>
</tr>
<tr>
<td>RR</td>
<td>Respiratory rate (breaths per minute; bpm)</td>
</tr>
<tr>
<td>Rsrs</td>
<td>Respiratory resistance, measured by FOT (cm.L.s⁻¹)</td>
</tr>
<tr>
<td>RSV</td>
<td>Respiratory syncytial virus</td>
</tr>
<tr>
<td>RV</td>
<td>Residual volume (Litres; L; or expressed as z-scores calculated from a reference set; zRV)</td>
</tr>
<tr>
<td>RV/TLC</td>
<td>Ratio of residual volume to total lung capacity; values greater than 30% (or 0.3) are indicative of hyperinflation and gas trapping.</td>
</tr>
<tr>
<td>RVRRTC</td>
<td>Raised volume rapid thoracoabdominal compression technique, infant spirometry</td>
</tr>
<tr>
<td>Sacin</td>
<td>Ventilation efficiency within the acinar lung zone or small airways (per Litre; L⁻¹)</td>
</tr>
<tr>
<td>Scond</td>
<td>Ventilation efficiency within the conducting airways or larger airways (per Litre; L⁻¹)</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation; SD is a measure of the spread of the data, the more spread out the higher the SD will be</td>
</tr>
<tr>
<td>SF₆</td>
<td>Sulphur hexafluoride</td>
</tr>
<tr>
<td>SGA</td>
<td>Small for gestational age; birth weight less than -2 SD from the mean calculated from a reference set</td>
</tr>
<tr>
<td>sGₛₕaw</td>
<td>Specific airways compliance</td>
</tr>
<tr>
<td>SnIII</td>
<td>Normalised phase III slope from a tidal breath measured during an MBW</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>SpO₂</td>
<td>Arterial oxygen saturation as measured by pulse oximetry (percent; %)</td>
</tr>
<tr>
<td>SpO₂max</td>
<td>Maximal SpO₂</td>
</tr>
<tr>
<td>sR₂ₕₗₜ</td>
<td>Specific airways resistance</td>
</tr>
<tr>
<td>sR₂ₕₜ</td>
<td>Specific effective airways resistance (Kilopascals per second; kPa.s⁻¹)</td>
</tr>
<tr>
<td>sR₂₉ₜ</td>
<td>Specific total airways resistance (Kilopascals per second; kPa.s⁻¹)</td>
</tr>
<tr>
<td>STDP</td>
<td>Standard temperature and pressure, dry.</td>
</tr>
<tr>
<td>STOP-ROP</td>
<td>Supplemental therapeutic oxygen for pre-threshold retinopathy of prematurity</td>
</tr>
<tr>
<td>SV at AT</td>
<td>Stroke volume at the anaerobic threshold (millilitres; mL)</td>
</tr>
<tr>
<td>Te</td>
<td>Expiratory time (Seconds; s)</td>
</tr>
<tr>
<td>Term</td>
<td>Birth at 37 to 42 completed weeks of pregnancy</td>
</tr>
<tr>
<td>TGV</td>
<td>Thoracic gas volume (Litres; L); The absolute volume of gas in the thorax measured during bodyplethysmography; Can be expressed as iTGV (intrathoracic gas volume)</td>
</tr>
<tr>
<td>Ti</td>
<td>Inspiratory time (Seconds; s)</td>
</tr>
<tr>
<td>Ti/Ttot</td>
<td>The fraction of the breathing or duty cycle (Ttot) that occurs during inspiration.</td>
</tr>
<tr>
<td>TLC</td>
<td>Total lung capacity (Litres; L; or expressed as z-scores calculated from a reference set; zTLC)</td>
</tr>
<tr>
<td>TLCO</td>
<td>Transfer factor of the lung for carbon monoxide (CO). Also known as TLCO (millilitres per minute per millimetre of Mercury; mL.min.mmHg⁻¹; or expressed as z-scores calculated from a reference set; zDLCO).</td>
</tr>
<tr>
<td>Ttot</td>
<td>Total breathing or duty cycle; (Seconds, s)</td>
</tr>
<tr>
<td>V'CO₂</td>
<td>Carbon dioxide production (Litres per minute; L.min⁻¹ or mL.min⁻¹ or Litres per minute per kilogram; L.min.kg⁻¹ or mL.min.kg⁻¹)</td>
</tr>
<tr>
<td>V'E</td>
<td>Minute ventilation (Litres per minute; L.min⁻¹)</td>
</tr>
<tr>
<td>V'O₂</td>
<td>Oxygen consumption (Litres per minute; L.min⁻¹ or mL.min⁻¹)</td>
</tr>
<tr>
<td>V'O₂max</td>
<td>Maximal V'O₂ (Litres per minute; L.min⁻¹ or mL.min⁻¹ or Litres per minute per kilogram; L.min.kg⁻¹ or mL.min.kg⁻¹)</td>
</tr>
<tr>
<td>V'O₂peak</td>
<td>Peak V'O₂ (Litres per minute; L.min⁻¹ or mL.min⁻¹ or Litres per minute per kilogram; L.min.kg⁻¹ or mL.min.kg⁻¹)</td>
</tr>
<tr>
<td>Va</td>
<td>Alveolar volume (Litres; L; or expressed as z-scores calculated from a reference set; zVa)</td>
</tr>
<tr>
<td>VC</td>
<td>Vital capacity (Litres; L)</td>
</tr>
<tr>
<td>V'CO₂max</td>
<td>Maximal V'CO₂</td>
</tr>
<tr>
<td>V'E/MVV</td>
<td>Ventilatory reserve or respiratory reserve</td>
</tr>
<tr>
<td>V'E/O₂</td>
<td>Ventilatory equivalent for O₂, also known as EqO₂</td>
</tr>
<tr>
<td>V'E/V'CO₂</td>
<td>Ventilatory equivalent for CO₂</td>
</tr>
<tr>
<td>V'Emax</td>
<td>Maximal V'E</td>
</tr>
<tr>
<td>VICS</td>
<td>Victorian Infants Collaborative Study <a href="http://www.vics-infantstudy.org.au">www.vics-infantstudy.org.au</a></td>
</tr>
<tr>
<td>VLBW</td>
<td>Very low birth weight; birth weight less than 1500 grams</td>
</tr>
<tr>
<td>VmaxFRC</td>
<td>Maximal flow at FRC, measured by RVRTC</td>
</tr>
<tr>
<td>V'O₂ at AT</td>
<td>V'O₂ at the anaerobic threshold (Millilitres per minute; mL.min⁻¹)</td>
</tr>
<tr>
<td>V'O₂/Work</td>
<td>Peak aerobic work rate. The relationship between V'O₂ and work rate during progressive exercise reflects the efficiency of aerobic metabolism to provide energy.</td>
</tr>
<tr>
<td>VP</td>
<td>Very preterm; infants born less than 32 completed weeks of gestation</td>
</tr>
<tr>
<td><strong>Vt</strong></td>
<td>Tidal Volume (Litres; L)</td>
</tr>
<tr>
<td><strong>Vtmax</strong></td>
<td>Maximal Vt</td>
</tr>
<tr>
<td><strong>Workmax</strong></td>
<td>Maximal work rate achieved during cardiopulmonary exercise (Watts; W), also known as Wmax</td>
</tr>
<tr>
<td><strong>Xrs</strong></td>
<td>Respiratory reactance, measured by FOT (cm.L.s(^{-1}))</td>
</tr>
<tr>
<td><strong>Xrs(_{4-24})</strong></td>
<td>Respiratory reactance at 4-24 Hz, measured by FOT</td>
</tr>
<tr>
<td><strong>Z</strong></td>
<td>Z-score; calculated as (actual value – predicted value)/standard deviation. The further a z-score moves from zero (mean) the further from “normal” it moves</td>
</tr>
<tr>
<td><strong>zHeight</strong></td>
<td>Height z-score; calculated using World Health Organization Child Growth Standards <a href="http://www.who.int/childgrowth/en/">http://www.who.int/childgrowth/en/</a></td>
</tr>
</tbody>
</table>


. . . unfinished, sent before my time into this breathing world, scarce half made up . . .

(Shakespeare, Richard III, Act I, Scene I)
5 Literature review

This thesis focuses on lung function and exercise capacity from a population of EP or ELBW survivors born from 1st January 1991 through to 31st December 1992, including those who had ‘newer BPD’ as a neonate. In addition, the possible contribution of growth restriction to the lung function and exercise capacity will be determined.

5.1.1 Normal respiratory embryology

The development of the respiratory system may be divided into five distinct stages, (embryonic, pseudoglandular, canalicular, saccular and alveolar; Figure 1). Lung growth starts in the fetus in the first 7 weeks, known as the embryonic phase. The lung, which provides surface area for gas exchange, begins development with a ventral diverticulum from the foregut during the fourth week of gestation.(1-3) Endoderm will develop into the airways and alveolar membranes, whereas the mesenchymal elements will develop into smooth muscle, cartilage, connective tissues and vessels.

Figure 1: A diagram illustrating the airway structure in the lung and the period in which each develops. (Adapted from (2))

The pseudoglandular phase of development takes place from approximately 7-17 weeks of gestation and is an important stage for the development of conducting airways. By 16 weeks the pre-acinar airway branching pattern is completed with the epithelium-lined lung bud branching into the surrounding mesenchyme producing airways seen in the adult lung.(1,2) The development of the pre-acinar pulmonary circulation runs in parallel with the development of the conducting airways (Figure 2).
The canalicular phase of development follows between 17 and 27 weeks. Lung morphology dramatically changes during this stage, including continuing formation of the respiratory airways and thinning and differentiation of the blood gas barrier. These gas exchange areas of the lung can be distinguished from the conducting zones within the developing lungs. During this phase of development, capillaries come into close contact with the surface epithelium of the developing airways, Figure 3 (1,2) Differentiation of type II epithelial cells and pulmonary surfactant synthesis begins. Surfactant consists of lipids and proteins; it lines the air-liquid interface in the alveoli and stabilises the alveolar surface to prevent collapse, particularly during expiration. The new blood vessels form by vasculogenesis of capillaries in the mesenchyme and sustained addition of the newly formed tubes to the existing vessels.(2) Vascular growth is closely linked to lung growth, thus inhibition or interruption to alveolar growth directly impairs vascularisation.(1,2,4)
Although gas exchange can occur from around 22 to 23 weeks’ gestation, true alveoli do not appear until about 28-30 weeks.\(^{(1,2)}\) By 24 weeks, around 17 generations of airway subdivisions are formed. During the next phase (terminal sac or saccular) between 28 weeks’ gestation to term, lung development transitions from the canalicular to the saccular phase where the pre-acinar airways grow, additional respiratory bronchioles develop, and acini begin to form (Figure 4). There is a gradual thinning of the pulmonary interstitium and thus the air-blood transfer possible, after thin walled terminal saccules have developed at the ends of the respiratory bronchioles. Alveolar saccules are lined with type I cells and lie alongside the pulmonary capillaries forming an extensive and effective gas exchange area. Alveolar type II cells comprise approximately 5-10% of the alveolar surface and are important for production of surfactant that is required for lung stability. Surfactant is first detectable at 24-25 weeks’ gestation. Surfactant is important for normal lung function in babies after birth.
During the initial 4 months of gestation, the airways are a template for pulmonary blood vessel development such that the vessels form around the branching airways. The increase in the total cross sectional area of the pulmonary vascular bed leads to an overall reduction in pulmonary vascular resistance.

The entire lung is well vascularised by 4 months, making gas exchange via diffusion possible. During the last 3 months of gestation, alveolarisation is extremely rapid, such that 100-150 million alveoli (representing 30-50% of the adult complement) are present by 40 weeks’ gestation, i.e. term. Airway growth continues after birth with diameter and length doubling or tripling until adulthood. Evidence from family studies of arterial branching patterns suggests there is a genetic influence on airway development. Although airway development is essentially complete by term, alveolar development is largely a postnatal process. However, the extent and duration of alveolar development during early childhood remains unclear. At birth, the lungs have a small volume relative to body surface area. From birth until around 3 years of age, lung volume increases mainly due to the increasing number of alveoli, then following complete alveolarisation of the lung parenchyma, lung volume increases by expansion of the alveoli. In contrast, the number of conducting airways is complete by 40 weeks and from then on they increase in size only. In healthy adults, alveolar volume is relatively constant, where the numbers of alveoli are in proportion with lung size. There are anatomical data on the airway growth in humans but airway size can be inferred from physiological measures of flow. Lung function increases in healthy children reaching a maximum in late adolescence/early twenties, and then begins to decline steadily with age (Figure 5).
During the first 20 to 25 years of life, the lungs continue to grow and mature. The maximal number of alveoli is reached in late school age and, from there on, the maturation of the respiratory system accelerates until an ultimate level of lung function is reached at approximately 20-25 years of age. For the remainder of life, the aging process is associated with a progressive reduction in lung performance; however, in the absence of lung disease, the respiratory system remains capable of maintaining adequate gas exchange for the entire lifetime. Physiological changes that are associated with aging include a decrease in the elastic recoil of the lung, a decrease in compliance of the chest wall (stiffening) and a decrease of strength of the respiratory muscles. These modifications of the chest wall not only alter compliance but also change the curvature if the diaphragm, this will affect its ability to generate force.

Any disturbance to the natural, normal sequence of lung growth and development will have a detrimental effect on the individual’s ability to reach their maximal lung structure and functionality, whether the disturbance occurs prenatally, antenatally or postnatally.

Given this pattern of lung development, it is not surprising that prenatal and early postnatal factors have important effects on airway function that can be identified throughout childhood and into adult life. Furthermore, any factor that substantially affects normal airway growth that occurs in childhood is likely to adversely affect adult lung function outcomes.

The increase in lung function during childhood and adolescence and subsequent fall in adulthood with growth and aging is a factor in the changing rates of respiratory morbidity that show the inverse relationship, i.e. increased in early childhood and later adulthood, and decreased
at other times, but also highlights important influences from development and the environment on long-term respiratory health. In other words there are other factors that may affect lung growth postnatally.

5.1.1.1 Asthma

Asthma is a common chronic respiratory illness in children and adults that is characterised by symptoms of wheezing, and breathlessness with narrowing of the airways from a reduction or obstruction of airflow. Asthma is characterised by reversible airflow obstruction, which can be either spontaneous or follows treatment e.g. with bronchodilators. The high degree of reversibility in airflow obstruction may be a marker of poorly controlled asthma. Anti-inflammatory treatment, e.g. inhaled corticosteroids, may improve the respiratory symptoms associated with asthma and may reduce chronic inflammation in the airways of asthmatic subjects. Persistent airway inflammation may influence normal lung growth during childhood and adolescence, and thus reduce the optimum level of lung function achieved by early adulthood. Asthma is by definition a chronic disease with reversible airflow obstruction. As the role of inflammation in asthma is increasingly understood, recent studies have suggested that asthma may lead to chronic, irreversible airflow obstruction. Some asthmatics, especially those with severe, persistent disease are at risk of impaired lung function growth and development in childhood, and excessive decline in lung function in adulthood, which may lead to life-threatening lung function impairment.

Preterm birth is associated with BPD and the development of asthma-like symptoms later in childhood. The long-term risk of asthma in preterm survivors, however, is not clear, but it is increasingly important to determine, as more preterm subjects are entering adulthood. Proposed mechanisms where preterm birth may influence subsequent risk of asthma involve genetic, perinatal and environmental factors. Preterm birth results in the loss of complexity of the normal lung structure, and greater susceptibility to subsequent injury from infection and environmental factors such as cigarette smoking. It is possible that preterm birth and asthma have shared genetic determinants.

5.1.1.2 Tobacco Smoke

Smoking exposure is defined by exposure of a person (or persons) to smoke generated from burning tobacco, most commonly in the form of cigarettes. This can be further stratified by the mode of either exposure, active (voluntary) or passive (involuntary). Cigarette smoking-related disease makes up the largest preventable cause of death and disease in Australia. It is a major risk factor for cardiovascular disease, as well as a range of cancers and other diseases and conditions. Diseases related to cigarette smoking are a major cause respiratory morbidity and mortality in adults. Respiratory disease in the presence of smoking exposure may begin before birth in childhood.
Smoking in pregnancy has been linked to LBW, which in turn is linked to later respiratory morbidity. Several studies have suggested that lung function and growth may be adversely affected by maternal smoking during pregnancy. These studies have shown abnormalities in lung function in infants exposed to maternal smoking. At present, there are not sufficient longitudinal data to show whether these harmful effects are short-lived, or whether they continue into adulthood. Maternal smoking (or in utero exposure to cigarette smoke) is associated with abnormalities in lung function at birth that may persist into adulthood in some studies. Passive smoke exposure may occur to the fetus through the placental circulation (in utero). Passive exposure to cigarette smoke may also occur in infancy and childhood. Active cigarette smoke exposure may occur in children and adolescents who take up cigarette smoking. Research has shown environmental tobacco smoke exposure during childhood adversely affects lung function, and especially variables reflecting airflow, e.g. FEV₁ and FEF25-75.

Several studies investigating the effects of passive and active smoking on the progression of lung disease in preterm cohorts have found passive smoking was associated with reduced airflow and air trapping as young adults, but only one study has reported similar findings earlier in childhood. The risk of adult chronic obstructive pulmonary disease will increase with further insults such as cigarette smoking.

There are few studies that have evaluated changes in longitudinal lung function in infancy relative to early smoke exposure. Le Soeuf et al. measured VmaxFRC (a measure of airflow) at 2-6 weeks of age and found it was reduced by a mean of 33 [SD12.3] mL, p=0.008 in infants whose mother smoked during pregnancy. Le Souef et al. followed-up these infants at 1 year of age and found the same pattern of reduction in VmaxFRC, in those exposed to maternal smoking. Distinguishing the effects of in utero exposure from all the other postnatal exposures in this setting is difficult.

From the published literature it appears those who have had cigarette smoke exposure are at risk of poorer lung function in adulthood, and may have a steeper rate of decline in lung function, especially those with low birth weights.

5.1.2 Respiratory function changes during infancy and beyond

Infants have relatively large surface area to body mass ratio and rapid growth over the first few years so their oxygen consumption and metabolic rate are relatively high when compared with adults, therefore their ventilatory requirement per unit of lung volume is increased. In the first few months of life infants increase their respiratory rate to meet the demands for oxygen in relation to body size. Infants are obligate nose breathers; nasal resistance represents
approximately 50% of total airways resistance. In the first year of life there is rapid lung and somatic growth. Alongside this are important developmental changes in respiratory physiology, especially of the upper airways, and with the highly compliant chest wall and dynamic elevation of functional residual capacity (FRC). (27) At the end of expiration, intra-pleural pressure is considerably less in an infant or an elderly person compared with a young adult. (9) In the older person this is because of emphysematous-like changes with loss of elastic recoil, compared with an infant with a chest wall that is extremely compliant, with more cartilaginous ribs, but with similar elastic recoil to an adult. (9) Therefore, there is minimal outward recoil with which to keep the lungs and airways expanded. (9) This results in FRC instability and a tendency for peripheral airway closure during tidal breathing, which in turn impairs gas exchange and ventilation/perfusion, rendering the infant or young child especially susceptible to airway obstruction and wheezing. Alongside changes in tidal breathing infants can use laryngeal braking and diaphragmatic activity post inspiration to brake (or slow) the expiratory flow.

5.1.2.1 Measures of respiratory function and exercise capacity

Basic concepts of normal pulmonary physiology that are involved in pulmonary function testing include mechanics (airflows and lung volumes), the ventilation-perfusion interrelationship, diffusion and gas exchange, and respiratory muscle or bellows strength. Ventilation is the process of generating the forces necessary to move the appropriate volumes of air from the atmosphere to the alveoli to meet the metabolic needs of the body under a variety of conditions. Simply, the contraction of the diaphragm and other inspiratory muscles expands the thorax, generating negative pressure in the pleural space. One component of pleural pressure, known as trans-pulmonary pressure, causes a flow of air into the airways and lungs (inspiration). When the trans-pulmonary and alveolar pressures equilibrate, airflow stops, the inspiratory muscles relax, and the lungs and chest wall elastic recoil raise pleural pressure, forcing air out of the lungs (expiration).

With a forced exhalation, the early portion of the blow is characterised by high flows, mostly from large airways, and the latter portion is characterised by low flows with a larger contribution from the smaller airways. Forced inspiration is generally not flow limited and is a function of overall muscular effort. (9) In contrast, a variety of factors affect expiratory flow, including the overall driving pressure, airway diameter, overall distensability of the lungs and chest wall, dynamic airway collapse (from a flow-limiting segment), and muscular effort. The overall driving pressure is the pressure head at the alveolus, or PALV, which is the difference between pleural pressure (PPL) and negative trans-pulmonary pressure (PTP), Equation 1.

\[
\text{Equation 1: PALV} = \text{PPL} - \text{PTP}
\]

The mechanism for the maximal expiratory airflow limitation seen in normal airways is a result of the gradual drop in pressure inside the conducting airways from the alveoli to the mouth,
this creates a trans-mural pressure gradient with the pleural pressure. This can cause dynamic airway compression and narrowing or closure of airways that have lost elastic recoil support from the lung parenchyma.

Pulmonary function studies use a variety of manoeuvres to measure and record the properties of four lung components. These include the airways (large and small), lung parenchyma (alveoli, interstitium), pulmonary vasculature, and the bellows-pump mechanism. Various diseases can affect each of these components.

5.1.2.1.1 Spirometry

Spirometry is the most commonly used lung function screening study. It generally should be the clinician's first option, with other studies being reserved for specific indications. Most patients can easily perform spirometry when coached by an appropriately trained scientist. The indications for spirometry are diverse; it can be used for diagnosing and monitoring respiratory symptoms and disease, for preoperative risk stratification, and as a tool in epidemiologic and other research studies.

Spirometry requires a voluntary manoeuvre in which a seated patient inhales maximally from tidal breathing to total lung capacity, and then rapidly exhales to the fullest extent until no further volume is exhaled at residual volume (Figure 6). The manoeuvre may be performed in a forceful manner to generate a forced vital capacity (FVC).

A spirogram is a graphic representation of air movement shown as a volume-time tracing or as a flow-volume tracing (Figure 6). Values produced in a spirogram provide important graphic and numeric data about the mechanical properties of the lungs, including airflow (FEV₁, forced expiratory volume in 1 second) and exhaled lung volume. The measurement is normally expressed in litres for volumes or in litres per second for flows, and is corrected for body temperature and pressure (BPTS) of gas that is saturated with water vapour. Data from a spirogram show important patterns that help distinguish obstructive pulmonary disorders that typically reduce airflow, such as asthma, from restrictive disorders that typically reduce total lung volumes, for example muscle weakness.
A number of spirometry standards have been developed over the years. The American Thoracic Society and European Respiratory Society have published standardised guidelines for acceptability and reproducibility criteria. A well-trained respiratory function scientist usually prepares the subject through the testing until the reproducibility of certain parameters suggests the results represent the best possible measure of lung function.

Gender differences exist in chest size and lung volume, and therefore lung function outcomes differ between the genders. Therefore, the gender differences seen in lung function are related to anatomical features of the thorax rather than the lungs per se. Males matched for standing height with females will have larger lung volumes and capacities. Males are therefore able to produce larger airflows compared with age and height matched females. (These gender differences are highlighted in Figure 9 and Figure 10.)

Abnormal spirometric studies generally are categorised as restrictive or obstructive abnormalities. An obstructive component implies airway obstruction, characterised by reduced expiratory flow rates. A restrictive pattern suggests a condition in which vital capacity (volume) is diminished. This must be distinguished from obstructive disease, diagnosed by measurement of normal or increased total lung capacity and decreased flow rates. The parameters obtained in spirometry are usually used to identify an obstructive pattern; the FEV₁ is the most studied because it is easy to measure, is reproducible and is sufficiently sensitive. This parameter is reduced in obstructive and restrictive disorders. In obstructive diseases, FEV₁ is decreased disproportionately to the FVC, reducing the FEV₁/FVC ratio indicating airflow limitation. In restrictive disorders, the FEV₁, FVC, and total lung capacity are all decreased, and the FEV₁/FVC ratio is normal or even high. FVC is a measure of lung volume and is typically reduced in diseases that cause the lungs to be smaller or reduce the amount of air a subject can inhale.
processes are generally termed restrictive and can include disorders of the lung parenchyma, such as pulmonary fibrosis, or of the ability to inhale, for example muscular weakness.

However, a reduced FVC is not always due to reduced total volumes and can be due to severe airflow obstruction and air trapping in large hyper-inflated lungs, as in emphysema. When this occurs, the FVC is reduced because of reduced airflow, air trapping, and increased residual volume. Reduced FVC can occur despite a normal or increased total lung volume. Therefore, FVC is not a reliable indicator of total lung capacity or restriction, especially in the setting of airflow obstruction.

The volume-time graphic and flow-volume curve establish the technical acceptability of a manoeuvre and therefore the quality of the data (Figure 8). The volume-time graphic is most useful in evaluating whether the end-of-test criteria have been met, whereas the flow-volume loop is most valuable in assessing the start-of-test criteria.

Figure 7: Spirometry patterns in various pulmonary disorders compared with normal, displayed as volume-time and flow-volume graphics

The shape of the flow-volume curve can indicate the location of airflow limitation, for example the large upper airways or smaller airways (Figure 8: Acceptable and unacceptable flow-volume loops and Back-extrapolation. To determine a new time-zero, back-extrapolation is performed using the steepest part of the slope on the volume-time curve, the PEF. This will minimize inaccuracies in FEV1 due to hesitation at the start of exhalation. (Adapted from (35))
With common obstructive airflow disorders, such as asthma, the disease usually affects the expiratory loop and can reduce the effort-dependent peak expiratory flow as well as subsequent airflows that are independent of effort. The expiratory loop is typically concave in this instance. In contrast, several anatomic disorders that narrow the large airways can produce a variety of patterns of shortening or flattening of either the expiratory or inspiratory loop of the curve (variable upper airway obstruction) or both loops of the curve (fixed upper airway obstruction). Other parameters reflect small airways, such as measures of flow from a spiromgram, such as the maximal mid-expiratory flow (MMEF) or forced expiratory flow at 25% to 75% vital capacity (FEF_{25-75}). The FEF_{25-75} is the slope of the spiromgram when between the 25% and 75% of the FVC has been expired. The FEF_{25-75} is a more sensitive early indicator of airway obstruction, but it is less reproducible. (28)
Figure 8: Acceptable and unacceptable flow-volume loops and Back-extrapolation. To determine a new time-zero, back-extrapolation is performed using the steepest part of the slope on the volume-time curve, the PEF. This will minimize inaccuracies in FEV₁ due to hesitation at the start of exhalation. (Adapted from [35])

Forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) increase up to around 20 to 25 years of age, then diminish with advancing age (Figure 9).(36) The annual rate of decrease in FEV₁ ranges from 20-40mLs per year after the age of 20 to 25 (Figure 9).(36)

Figure 9: Evolution of forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) as a function of age. (Adapted from (19))

There are characteristic changes in the flow volume curve with ageing (Figure 5).(36) The changes in the curve suggest alterations in the small peripheral airways, with an obstructive pattern presents even in those who have never smoked cigarettes, implying this pattern may be
normal in advancing age. After the age of 20 to 25 years of age peak flow rates tend to decrease. The variability in predicted peak flow is very large making comparison to prediction equations unreliable.

**Figure 10:** Evolution of forced expiratory flow between 25% and 75% of FVC (FEF25-75%) as a function of age. (Adapted from [19])

Another important measurement is airways resistance (Raw); this is the ratio between alveolar pressure and airflow obtained during quiet breathing.[30,37,38] Raw can be measured in several ways; plethysmography is considered the ‘gold standard’ for measuring airway resistance.[30,32,37,38]

Although FEV₁ and Raw measurements generally agree, they are complementary, as Raw may be more sensitive to variation in airway size.[30] Resistance decreases as lung volume increases with growth, therefore after adjusting for lung volume, age has no significant effect on Raw. Specific airways resistance (sRaw) is the value of Raw multiplied by functional residual capacity (FRC)—or Raw multiplied by intra-thoracic gas volume (TGV) measured by plethysmography. The measurement takes place as the subject breathes normally through the plethysmography mouthpiece, and is displayed on an x-y graph, the y-axis displays flow at the mouth and the x-axis displays the volume shift that occurs during inspiration and expiration due to differences in the humidity and temperature (Figure 11).
Figure 11: Graphic of a total specific airways resistance ($sR_{tot}$) and effective specific airways resistance ($sR_{eff}$) loops. Mouth airflow is plotted on the y-axis with inspiratory flows positive and expiratory flows negative. Shift volume is plotted on the x-axis with inspiratory shift volumes positive and those during expiration negative. (Adapted from [39])

TGV is the largest determinant of $R_{aw}$ and, although the correction of $R_{aw}$ for lung recoil pressure may be physiologically more suitable, for ease, it is usually corrected for lung volume. (39) Because the $sR_{aw}$ loop (Figure 11) varies across each tidal breath, different researchers have used different parts of the $sR_{aw}$ loop to approximate the $sR_{aw}$ for the entire tidal breathing cycle. (39) The total specific resistance ($sR_{tot}$) and effective specific resistance ($sR_{eff}$) are examples of these partial estimates of $sR_{aw}$ that are commonly used in clinical laboratories. (39) The $sR_{tot}$ is calculated from a straight line between maximal inspiratory and maximal expiratory shift volume points on the graph (Figure 11). (39) $sR_{tot}$ is sensitive to obstructive changes in the peripheral airways, but is subject to wide variability because it takes its measurements from the extremes of the tidal breath, i.e. maximal and maximal expiratory points of the shift volume. (39) $sR_{eff}$ attempts to integrate the effects of variable flows and volume shifts that occur during tidal breathing. (39) $sR_{eff}$ integrates the volume of a tidal breath versus the volume shift of the tidal breath and the volume of a tidal breath versus the flow of the tidal breath, which allows for a better assessment of the airway behaviour during the entire tidal breath. (39) Goldman et al. suggest that $sR_{eff}$ reflects larger central airways somewhat more prominently than $sR_{tot}$. (39)

In normal subjects, the decreasing size of the peripheral airways is adequately compensated by the increasing number of airways at each generation. (30) Therefore, during quiet breathing, the main areas of resistance in the lung are the trachea and the larger airways. (30) This means that the evaluation of airway resistance is more sensitive to alterations in large airways, but relatively insensitive to changes in the small airways, also defined as the ‘silent zone’ within the lungs. (30) Equally, forced expiratory flows are more sensitive to changes in the small airways. Although the evaluation of $R_{aw}$ seems to be less reproducible when compared with FEV$_1$, it is more sensitive to changes in airway calibre, as revealed by very impressive changes when performing methacholine challenge or beta$_2$-agonist response. (40-42) Van Noord et al. showed that more subjects are responsive to a bronchodilator when assessed by $R_{aw}$ compared with FEV$_1$ (limits of
agreement: 21% for $R_{aw}$, 13% for FEV$_1$), because of the greater sensitivity of the $R_{aw}$ technique.(30) Plethysmography $R_{aw}$ can be measured during quiet breathing. Because no active cooperation is required, $sR_{aw}$ measurements can be performed from two years of age.(30,43)

There are other methods, but they are used less.(30) The oesophageal balloon technique measures airway and lung tissue resistance. It is particularly uncomfortable and unsuitable for repeated or prolonged measurements; additionally, its variance is very high.(30)

The forced oscillation technique (FOT), is another way to measure $R_{aw}$, it measures the total thoracic resistance ($R_{rs}$, respiratory resistance and $X_{rs}$, respiratory reactance), but it does not provide information about flow, nor does it distinguish between restrictive and obstructive changes, or intra- and extra-lung disorders.(30,32) The $R_{rs}$ is not the same but is similar to $R_{aw}$ measured in the body plethysmograph. The $X_{rs}$ is an estimation of the compliance of the respiratory system and is influenced by the forces from the lung tissue, chest wall and air within the lungs.

The interruption method ($R_{int}$) is used less frequently, and it also measures a component of extra-pulmonary resistance, but is less reproducible and not as sensitive as other methods.(30,44)

### 5.1.2.1.2 Lung volumes

Spirometry does not measure residual volume (RV), functional residual capacity (FRC; resting lung volume), or total lung capacity. Vital capacity (VC) is a simple measure of lung volume that is usually reduced in restrictive disorders; however, reduction in the VC measured during spirometry should prompt measurement of lung volumes to confirm the presence or absence of a true restrictive ventilatory disorder.

The term lung volume refers to the volumes of gas or air within the lungs as measured by body plethysmography, Figure 12, or by gas dilution methods.(9,38) In the measurement of lung volumes, the volumes are measured and capacities are calculated (Figure 6). The FRC is the volume of gas in the lung at the end of expiration during normal tidal breathing.(9,38) The expiratory reserve volume (ERV) is the volume of gas that can be maximally exhaled from the end-expiratory level during tidal breathing (i.e. from the FRC).(9,38) The maximum volume of gas that can be inspired from FRC is referred to as the inspiratory capacity (IC).(9,38) The inspiratory reserve volume is the maximum volume of gas that can be inhaled from the end-inspiratory level during tidal breathing.(9,38) RV refers to the volume of gas remaining in the lung after maximal exhalation.(9,38) Body plethysmography is a method of measuring lung volume that uses the principle of Boyle's law, which states that the volume of gas at a constant temperature varies inversely with the pressure applied to it.(9) One advantage of body plethysmography is that it can measure the total volume of air in the chest, including trapped gas.(9) Another advantage is that
this test can be performed quickly. One disadvantage is the complexity of the equipment. For the
test, the subject sits in a closed body box of known volume (Figure 12).(9) From the FRC, the
patient inhales against a closed shutter, this produces changes in the box pressure proportional to
the volume of air in the lungs.(9) The volume measured by this technique is referred to as thoracic
gas volume (TGV) and represents the lung volume when the shutter was closed, approximately
FRC.(9) After the FRC is measured, measurement of lung subdivisions (inspiratory capacity,
expiratory reserve volume, vital capacity) follows, while the patient is still on the mouthpiece.(9)
From these volumes and capacities, the residual volume and total lung capacity (TLC) can be
calculated.(9) Residual volume (RV) is the volume that remains after maximal expiration.(9)

Figure 12: Lung volumes as measured by body plethysmography.(45)

5.1.2.1.3 Diffusing capacity of the lungs

Gas exchange is the primary function of the lung, and many patients with pulmonary
disease have impaired gas exchange that can progress to respiratory failure and death.(9) External
respiration occurs between alveolar gas and pulmonary capillary blood; internal respiration occurs
between systemic capillary blood and tissue.(9) Arterial blood gas measurements reflect the
balance between internal and external respiration.(9) Ventilation is composed of gas that respires
(alveolar ventilation) and gas that does not respire (dead-space ventilation).(9) The balance
between alveolar ventilation and the CO₂ production is shown in the arterial PCO₂ value.(9) The
arterial PO$_2$ shows the adequacy with which the pulmonary blood flow is oxygenated by the lungs.\(^{(9)}\)

Diffusion is limited by the surface area over which diffusion occurs, capillary blood volume, haemoglobin concentration, and the properties of the lung parenchyma, for example alveolar-capillary membrane thickness and/or the presence of excess fluid in the alveoli.\(^{(9)}\) The total lung volume is not involved in gas exchange. Most gas exchange occurs as a function of diffusion, not bulk flow. The role of ventilation is to provide bulk flow of gas with the ambient air and to provide a constant gradient for oxygen and carbon dioxide.\(^{(9,46,47)}\) Spirometry measures various parts of bulk flow. Diffusing capacity measures the forces at work in molecular movement, with the oxygen concentration gradient being from the alveolar surface through to the haemoglobin molecule. The test, diffusing capacity of the lung, commonly uses carbon monoxide as the tracer gas for measurement because carbon monoxide has a high affinity for binding to the haemoglobin molecule.\(^{(9)}\) This allows a measurement of pure diffusion, such that the movement of the carbon monoxide only depends on the properties of the diffusion barrier and the amount of haemoglobin.\(^{(9)}\) The properties of oxygen and its relatively low affinity for haemoglobin compared with carbon monoxide make it perfusion dependent; thus, cardiac output can influence actual measurements of oxygen diffusion measurements.\(^{(9,47)}\)

Diffusing capacity of the lung for carbon monoxide (DL$_{CO}$) is the measure of carbon monoxide transfer.\(^{(47)}\) In Europe, it is frequently called the transfer factor of carbon monoxide (TL$_{CO}$). The commonly used clinical tests to measure DL$_{CO}$ are based on a ratio between the uptake of carbon monoxide in millilitres per minute divided by the average alveolar pressure of carbon monoxide at standard temperature and pressure, dry, per minute (STDP).\(^{(46)}\)

Measurement of alveolar volume (VA) and pulmonary DL$_{CO}$ can provide a functional assessment of the volume and surface area available for gas exchange, which indirectly estimates the alveolar number and size.\(^{(3)}\) In subjects from around late school age to adulthood, DL$_{CO}$ and VA increase with somatic growth, such as height. These physiologic results are consistent with morphometric data that parenchymal lung growth occurs in this age range primarily by the increasing size of the existing alveoli.\(^{(2,3)}\) Ageing is associated with a decline in the diffusing capacity of the lungs for carbon monoxide (DL$_{CO}$). The annual reduction in DL$_{CO}$ has been estimated to range from 0.2-0.6 mL/min/mmHg.\(^{(47)}\) This decrease is more apparent after 40 years of age. Factors that influence the diffusing capacity of the lung include increased ventilation-perfusion mismatch, reduction of alveolar surface area for gas exchange, decreased density of pulmonary capillaries and a reduction in lung capillary blood flow.\(^{(48)}\) Interstitial lung diseases may result in abnormal DL$_{CO}$ long before spirometry or lung volume abnormalities are evident. Reduced DL$_{CO}$ is not only an abnormality of restrictive interstitial lung disease but also can occur in emphysema. Therefore other obstructive processes that mostly affect the airways can have...
similar spirometry, but a reduced DL\textsubscript{CO} implies a loss of alveolar surface area consistent with emphysema.

The most commonly used and standardised technique to measure DL\textsubscript{CO} is the single-breath breath-holding technique.(46) In this test, a subject breathes in a known volume of tracer gas that typically contains 10% helium, 0.3% carbon monoxide, 21% oxygen, and the balance nitrogen.(46) The subject then exhales to wash out the mechanical and anatomic dead space, after which an alveolar sample is collected. DL\textsubscript{CO} is calculated from the total volume of the lung, breath-hold time, and the initial and final alveolar concentrations of carbon monoxide. The exhaled helium concentration is used to estimate a single-breath estimate of total lung capacity and the initial alveolar concentration of carbon monoxide. The driving pressure is assumed to be the calculated initial alveolar pressure of carbon monoxide.(9) The calculated DL\textsubscript{CO} is a product of the patient's single-breath estimate of total lung capacity multiplied by the rate of carbon monoxide uptake during the 10-second breath hold.(9)

Haemoglobin concentration is a very important consideration when interpreting reductions in DL\textsubscript{CO}.(33) DL\textsubscript{CO} may be decreased when the patient is anaemic. Because the level of haemoglobin in the blood and diffusing capacity are directly related, a correction for anaemic patients (DL\textsubscript{COc}) is used to further define whether a DL\textsubscript{CO} is reduced due to anaemia or due to parenchymal or blood-gas barrier limitation.

5.1.2.1.4 Ventilation efficiency within the lungs

The understanding and measurement of ventilation inhomogeneity is one of the most rapidly expanding areas in paediatric respiratory physiology. Mixing of the gas within the lungs with inspired gas is an essential requirement for effective respiration, i.e. we ventilate to get oxygen and to remove carbon dioxide from our alveoli. If this gas mixing within the lung in not uniform, inhomogeneous, or inefficient then an increase in ventilation is required to ensure there is adequate gas exchange. The efficiency of gas mixing within the lungs in dependent on the structure of the lung, especially in the peripheral regions, resistance to airflow (airway resistance) and lung compliance, or the distensability or floppiness of the lungs. The airways within the lungs are designed mix inspired gas efficiently with the resident gas, but as you descend the airway (Figure 1) there are many divisions, and not all these all uniform. The first 16 airway generations (Figure 1) are usually referred to as the conducting airways, where gas movement is accomplished mainly by convection, or bulk flow of gas and no gas exchange is able to take place. The remaining airway generations (Figure 1) are known as the acinar lung zone where gas exchange within the lungs takes place, and are made up of the respiratory bronchioles, with alveolar ducts budding.
from them and the acinus or alveoli, and ventilation is achieved mainly by diffusion. Another way of characterising the airway generations is to refer to the first 8 airway generations and larger more proximal airways and the remaining generations into the smaller or peripheral airways. The total cross-sectional area of the airway tree is narrowest around generations 3-5, and then significantly increases thereafter towards the lung periphery. Becklake et al. reported a “new index of the intrapulmonary mixture of inspired air” in 1952, which provided a measure of gas mixing efficiency or ventilation efficiency.(49) With recent advances in computer technology and analyser ability, the complex data analysis and fast gas concentration calculation have become more readily available. Commercial systems now exist and more researchers are using and reporting data relating to ventilation efficiency.

In a simple one-compartment lung, ventilation should be homogenous or even, where after inhalation, the air is evenly distributed, mixed and emptied from all areas of the lung. In reality, even healthy "normal" lungs exhibit some ventilation inhomogeneity, or uneven distribution and mixing of air within the lungs, due to inter- and intra-regional differences in ventilation. The presence of disease in airways or lung tissue may exaggerate these differences, resulting in less efficient respiration. The ability to measure the efficiency of ventilation within the lung offers an exciting potential to identify early lung disease processes that may be missed by conventional flow-based lung function measures, for example spirometry.(50) Multiple breath inert gas washout (MBW) is a non-invasive test, which requires normal tidal breathing only and is therefore feasible across all age groups; it offers improved sensitivity compared with spirometry to detect early lung disease throughout childhood.(50) There are many techniques for measuring MBW, most of which involve either washing out or washing in an inert gas. The longer this wash-in or washout takes the less efficient is the ventilation. The original MBW test involved washing out the resident inert gas present within the lungs, i.e. nitrogen. This is accomplished by getting the subject to tidally breath 100% oxygen until the gas concentration of nitrogen at the end of a tidal breath falls to 1/40th of the starting concentration; at this point nitrogen is considered to be washed out of the lungs. Various indexes are calculated from the differences between the start and finish gas concentrations, the cumulative volume from the washout, and the number of times the lung volume is washed out, to reach the final concentration.

Crawford et al. in 1985 proposed that analysis of the phase III slope measured during MBW would allow distinction of the ventilation heterogeneity within the acinar lung zone (peripheral) from that of the conducting airways (proximal). More complex analysis using the slopes generated during normal tidal breathing suggests that MBW may allow the area of ventilation inefficiency to be localised within the conducting airways (Scond), or within the acinar or gas exchanging zone of the lungs (Sacin). There is a zone within the lungs where ventilation by convection and ventilation by diffusion meet; this zone is known as the diffusion-convection front.
Different disease processes occurring within the lungs may move this diffusion-convection front peripherally or proximally, and thus alter the Scond and Sacin dependent upon where the disease is affecting ventilation efficiency. Phase III slopes are a plot of a single breath measured during the MBW test, and shows the expired volume of the breath along the x-axis and the concentration of expired gas as the expiration of that breath continues, in this case nitrogen concentration, Figure 13. As shown in Figure 13 there are different phases throughout the expired breath; firstly a very low expired gas concentration (phase I), then a rapid rise (phase II), followed by a plateau in the expired gas concentration (phase III).

Figure 13: A single breath washout curve from the MBW test, illustrating phase I, phase II, phase III and the alveolar phase III slope (red)

Phase I is the apparatus and airway dead space, phase II is the transition and phase III is known as the alveolar plateau and equates to approximately 65% to 95% of the tidal volume of an expired breath. The phase III slope is calculated by regression over this region of the expired breath and is the change in gas concentration over that tidal volume. To compare these slopes over the entire MBW is not possible as the expired gas concentration of each breath decreases as the MBW progresses, therefore the phase III slope is normalised for gas concentration, this is known as the normalised phase III slope or SnIII. The SnIII values for each breath of the MBW test can then be plotted against the lung volume turnover (cumulative expired volume/FRC) (Figure 14) Scond and Sacin are derived from analysis of concentration SnIII of a multiple breath inert gas washout.
Thompson et al. speculated that the Scond value might be the result of the remodelling process that occurred in chronic asthma that did not respond to treatment and the functional reflection of airway inflammation, within asthmatic airways. (51)

The ability to measure small airway function is important in a number of disease processes, for example cystic fibrosis, asthma and preterm lungs, all of which may result in changes within the small airways or acinar air spaces affecting airflow or ventilation efficiency within the airways. The small airway function variables measured in spirometry, such as FEF_{25-75\%} or forced expiratory flow at 50\% of FVC (FEF_{50\%}), may be reduced with the presence of small airways disease but there is mounting evidence that they are not sensitive or specific to disease processes occurring in small airways or airspaces, especially in the presence of airflow obstruction in the larger conducting airways or gas trapping within the lungs. (51-56)

5.1.2.1.5 Muscles of ventilation

The “muscles of ventilation” become especially important when the respiratory system is stressed, such as when exercising or with respiratory disease. The muscles of ventilation are often considered as three distinct groups: the diaphragm, intercostal muscles, and accessory muscles. (9)

The muscle fibres of the diaphragm originate and insert on the inferior surface of the lower ribs. (9) Motor innervation originates from the spinal cord at the third through fifth cervical roots, which combine to form the phrenic nerve. (9) The diaphragm is the major muscle of ventilation and it performs all the work associated with normal breathing; the other inspiratory muscles provide great reserve. (9) The external intercostal muscles lift the anterior chest wall and facilitate inspiration, whereas the internal intercostal muscles act in an opposite direction and play a role in forceful expiration. (9) The accessory muscles of ventilation serve to elevate and stabilize the chest wall in its greatest diameters and thereby improve the efficiency of diaphragmatic excursion. (9)
The major accessory muscles are the scalene, sternocleidomastoid, trapezius, and pectoralis.(9) Accessory muscles normally are inactive in the absence of exercise and stress. Inspiration is always an active muscular event, whereas expiration normally is passive; elastic recoil of the lung and chest wall provides the expiratory energy.(9) Abdominal muscles (external oblique, rectus abdominis, internal oblique, and transverse abdominis) play a major part in active expiration.(9)

Lung elasticity results from interstitial elastic fibres and alveolar surface tension, producing forces that act to collapse the alveoli.(9) La Place's law says that elastic forces increase as the radius decreases, meaning that smaller alveoli should collapse by emptying into larger alveoli.(9) This phenomenon is prevented by a pulmonary surfactant complex that reduces surface tension forces during expiration.(9) In general, every alveolus has a critical volume at which the distending forces are equal to the elastic forces; below this critical volume, the elastic forces are overwhelming and total collapse ensues; above this critical volume, the surfactant complex acts to balance the opposing distending and elastic forces.(9) The term compliance is used to describe forces opposing distortion from the resting state. Because lung elastic forces must be overcome to achieve inspiration, low lung compliance is associated most often with increased elastic forces.(9) FRC is determined by the static balance between the outward recoil of the chest wall and the inward recoil of the lung.(9)

5.1.2.1.6 Cardiopulmonary exercise testing

Maximum oxygen consumption ($V'O_2_{\text{max}}$) is widely recognised as the single best indicator of aerobic fitness.(57,58) Oxygen uptake ($V'O_2$) is determined by O$_2$ demand at a cellular level, as the work rate of the muscles increases and their energy requirement increases during exercise, the demand for O$_2$ will also increase.(58) The maximal rate of O$_2$ uptake is determined by the maximum rate that O$_2$ can be delivered to the lungs and the rate of transfer to the blood and tissues at a cellular level.(58) $V'O_2_{\text{max}}$ may be low or at the lower limit of normal for subjects who are unfit but otherwise well.(58)

The ability to perform physical exercise depends on the cardiopulmonary capacity to supply O$_2$ and clear CO$_2$ from the blood via the lungs. The cardiac and pulmonary systems work alongside each other to provide O$_2$ supply and CO$_2$ removal from the tissues. There are four major parts involved with this process:

1. Pulmonary ventilation, or the physical movement of air into and out of the lungs;
2. Pulmonary diffusion, or the exchange of O$_2$ and CO$_2$ between the lungs and the blood;
3. Transport of O$_2$ and CO$_2$ in the blood, dissolved and bound to haemoglobin;
4. Gas exchange of O₂ and CO₂ between the capillary blood and the working muscle.(9,58)

The main function of the cardiopulmonary exercise testing (CPX) is the functional assessment of O₂ consumption and CO₂ production during a physically stressed situation, i.e. exercise of increasing intensity.(9,58) The performance of CPX therefore provides data describing the performance capacity of the heart, lungs, pulmonary and circulatory vasculature, and the blood’s ability to transport and transfer O₂. The CPX test can also assist in isolating which physiological system(s) may be causing any impairment seen. Treadmill testing is favoured over cycle ergometry because it uses movements that are more habitual, is externally paced and does not need to be adjusted for stature.(58)

O₂ consumption and CO₂ production are measured whilst the subject breathes air (21% O₂) through a mouthpiece wearing a nose clip. O₂ and CO₂ are sampled from the tidal breathing and analysed using fast response gas analysers linked to computer software that allows breath-by-breath values for each of the gases. When performing CPX the subject will be fitted with a 12-lead electrocardiogram (ECG) to allow heart rate (HR) response to be measured as exercise intensity increases. CPX is usually performed on a motorised treadmill or a cycle ergometer. Treadmills are preferable in children to achieve maximal effort compared with cycle ergometry. Cycle ergometry is preferable in subjects with balance, gait or orthopaedic issues. Younger children can learn to walk and run on the treadmill relatively easily. A non-individualised increase in work, with large increments, such as the Bruce protocol, may lead to the premature cessation of exercise before cardiac or respiratory limits are reached, due to exhaustion of the muscles of the lower limbs, especially the quadriceps.(59,60) The duration of exercise (10 to 12 min) is sufficiently short not to discourage the child. There is a consistent relationship between exercise capacities when results are compared from both modes of exercise test, although cycle ergometry tends to produce lower peak O₂ consumption values, approximately 10-12% less when compared with treadmill tests, because less muscle mass is utilised in cycle ergometry.(57,61)

The protocol should be tailored to the individual to a fatigue-limited exercise test, with a total exercise time of between 8 and 12 minutes.(57) When the test duration is less than 6 minutes results may underestimate the maximum exercise capacity and work rate. Similarly, when the test is greater than 12 minutes the subject may stop the test due to specific muscle fatigue, such as sore calf muscles, rather than cardiopulmonary endpoints. Therefore exercise intensity should ideally be tailored to the fitness and clinical circumstances of each subject, and duration kept between 8-12 minutes regardless of baseline fitness levels.(59) The protocol used for exercise testing in this study was an individualised protocol based on that described by Karlia et al. and is described in further detail in Chapter 7.4.3.(58,59)
During a CPX test, as exercise intensity increases \( V'O_2 \) increases, alongside this initially the \( V'CO_2 \), HR and ventilation increase nearly linearly.\(^{(9,58)}\) During the initial stage of the CPX test energy for the muscles is primarily sourced from glycogen.\(^{(9,58)}\) The level of exercise intensity or work rate (Watts) will eventually get to a point as the CPX test continues where the energy requirements for exercise are no longer met solely by aerobic respiration and anaerobic metabolism plays an increasing role in energy supply.\(^{(9,58)}\) Anaerobic metabolism produces energy and increases the \( V'O_2 \) via chemical reaction between hydrogen ions \([H^+]\), from lactate] and dissolved \( CO_2 \).\(^{(9,58)}\) As the level of lactate increases \( H^+ \) levels increase (acidosis) and drives the reaction to the right and extra \( CO_2 \) is added to that produced aerobically and the \( V'CO_2 \) slope increases.\(^{(9,58)}\) The point where there is a change in the slope of the relationship between \( V'O_2 \) and \( V'CO_2 \) as exercise intensity increases is identified as the ventilatory threshold, i.e. the ventilatory threshold is the upper limit of exercise intensity for that subject that can be accomplished through aerobic ventilation.\(^{(9,58)}\) There are several other terms for ventilatory threshold, such as anaerobic threshold or lactate. For the purposes of this thesis, I will refer to this phenomenon as the anaerobic threshold. In normal subjects the anaerobic threshold would occur at approximately 50-60% of their predicted \( V'O_2\)max. \( V'O_2 \) at ventilatory threshold may be reduced in a wide range of clinical conditions and is a useful indicator for the level of fitness, indicating early onset of acidosis. Efficient gas exchange within the lungs is important for normal responses to exercise and is usually assessed by the alveolar-arterial partial pressure difference.\(^{(9,58)}\) As the oxygen consumption increases during the CPX test the lung must be able to increase its diffusive capacity in order to meet the demand and maintain the alveolar-arterial partial pressure difference.\(^{(9,58)}\) The increased diffusion of oxygen within the lung during exercise results from pulmonary capillary recruitment.\(^{(9,58)}\) If the lungs are diseased the impairment in gas exchange may result in shortness of breath.\(^{(9,58)}\) Subjects with a diffusion impairment that results from a thickened blood-gas barrier, such as pulmonary fibrosis or other interstitial lung disease, or who have an inability to recruit pulmonary capillaries, such as chronic obstructive pulmonary disease will have an increased alveolar-arterial partial pressure difference, which may result in a greater mismatch during CPX, leading to a reduced \( V'O_2\)max.

Ventilation and cardiac output increase with the increasing exercise intensity of the CPX test. The rise in minute ventilation (\( V'E \)) stems from increases in the frequency of breathing (BF) and the depth of each breath.\(^{(9,58)}\) Increasing \( V'E \) is one of the main ways the body regulates blood gases and acid-base status when the metabolic demands of exercising muscles increase, such as during exercise.\(^{(9,58)}\) In normal subjects tidal volume (\( Vt \)) increases lead to increased ventilation in the early phases of the CPX, as the test progresses both the \( Vt \) and BF increase until the subject reaches approximately 70-80% of their peak exercise level, thereafter the increased ventilation requirements are met mainly by increases in BF.\(^{(9,58)}\) The BF at rest varies from 12-16 breaths per minute and can increase to 40-50 breaths per minute at peak exercise.\(^{(58)}\) The
increased BF with CPX is accomplished through a decrease in inspiratory time (Ti) and expiratory time (Te), i.e. faster breaths with shorter inspiratory and expiratory times, although the ratio of Ti to the total breath cycle duration or the duty cycle only increases slightly during exercise, in normal subjects it is approximately 0.40 at rest and increases to approximately 0.50 during intense exercise.(9,58) The ventilatory reserve has been defined as maximal voluntary ventilation (MVV) or an estimate of MVV, such as FEV₁ multiplied by 37, and is typically reported as V'E as a percentage of MVV. MVV is the maximal amount of air a subject has breathed in and out within 1 minute; it is measured practically in subjects over a 15-second interval that is extrapolated to 1 minute. Typically in normal subjects’ peak V'E approaches 70% of MVV at maximum exercise, although this is subject to age and fitness, and those with ventilatory impairment use more of the ventilatory reserve.(9,58) Although increases in V'E above 70% of MVV require large respiratory pressures as the lung compliance is markedly decreased, this in turn leads to exaggerated respiratory discomfort and shortness of breath, i.e. large efforts are required to achieve small increases in the V'E above 70% MVV. The ventilatory reserve demonstrates how close to maximum V'E, i.e. ventilation demand, is achieved at maximum exercise where V'Emax approaches MVV. Common ventilatory indices reported provide information about changes to minute ventilation (V'E) and breathing pattern (Vt and BF), alongside the ventilatory reserve and alterations to ventilatory timing (Ti, Te and total time [Ti/TOT]). Ventilation efficiency is a balance of optimal breathing mechanics (airflow and diffusion) and gas exchange, therefore many of the indices of ventilation are combined, such as V'E versus V'O₂ and V'E versus V'CO₂. Peak HR may be estimated from various reference equations, the two most commonly used estimates are 220-Age and 210-(agex0.65), both give very similar answers.(9,58) If the subject reaches their predicted maximal HR it suggests that they have made a maximal or near maximal effort during the CPX test. HR in healthy subjects increases nearly linearly with V'O₂.(58) The Peak HR may be reduced in subjects with cardiopulmonary disease.(58) As exercise intensity increases each heart contraction must deliver an increasing quantity of oxygen to meet the demand of the working muscles, this is defined as the O₂ pulse.(62) Typically at rest the O₂ pulse of 2.5-4 mL per beat and increases to 10-15 mL per beat at peak exercise.(62) This is estimated from the ratio of V'O₂ to HR and reflects the amount of O₂ that is extracted by the muscles per heartbeat. Some researchers use O₂ pulse as an estimator of stroke volume during CPX.(62)

The determination of a technically acceptable CPX test requires maximal patient effort, where a V'O₂ max plateau is achieved, the maximal HR is greater than 90% of that predicted, the respiratory exchange ratio (V'CO₂/V'O₂) is greater than 1.05 and the subject is displaying signs of exhaustion. For the purposes of this thesis I will use the equation 220-Age to estimate maximum predicted heart rate as this is what we use currently in routine clinical exercise testing within the respiratory laboratory.
5.1.2.1.7 Normality and reference equations

Studies from healthy populations indicate that parameters of lung function, such as FEV$_1$ or FVC, are associated with standing height, age, gender, race, and, to a lesser extent, weight. Lung function has a normal distribution and a wide range of values may be considered normal. There is no absolute cut-off point for what is normal in humans; an arbitrary statistical approach is usually used to define abnormality. Regression equations have been generated by several investigators using different methodologies to study different populations.

Many methods have been developed to define the normal range of spirometry. These methods include using a fixed percentage of predicted, for example and arbitrary cut-off at 80% predicted, and a fixed FEV$_1$/FVC ratio, (<0.70), neither of these methods have a firm statistical basis, come from confidence intervals of very old data, and are not recommended.

The American Thoracic Society and European Respiratory Society recommend using a lower limit of normal by identifying the lowest 5% of a population, or patients that fall outside the limits of 1.96 standard deviations from the mean.

Weight is less important as a predictor of respiratory function. Obese patients may have abnormal spirometry (reduced FVC) because of the diaphragm’s inability to displace the intra-abdominal fat. Body weight has little impact on intra-thoracic gas volume.

Ethnicity plays an important role in defining normal lung function; it has been recognised that people of different races for any given height and age have different lung volumes. At present there are no reliable corrections for race.

5.1.3 Preterm birth

Preterm birth is the delivery of an infant before 37 weeks’ completed gestation. “Very preterm” infants (VP: those born prior to 32 weeks’ gestation) have higher mortality and morbidity rates than more mature infants, and “extremely preterm” infants (EP: those born prior to 28 weeks’ gestation) have even higher rates again. Over the past four decades advances in perinatal care have improved outcomes for infants born following short gestations. The survival rates of infants born at or near the limit of viability have improved. The number of completed weeks’ gestation is used to define whether a birth is preterm or a fetal loss; this is the threshold of viability. In Victoria, over the last 4 decades there has been a three-fold increase in the survival rates of ELBW babies. In the 1970s one-in-four ELBW babies survived compared with the 1990s where three-in-four survived. Current survival rates in Victoria are
approximately 70% on a regional basis. The increases in survival over the decades is attributed to improvements in neonatal care, such as exogenous surfactant, antenatal corticosteroids, gentler ventilation techniques and changing attitudes towards the viability of these babies. In addition, in Victoria, there has been a move to regionalised care where fewer EP/ELBW babies are born outside high level perinatal care facilities.

Mortality rates are highest in the most preterm, the rate decreases as gestational age increases and approaches term. Other studies have indicated that preterm birth is associated with higher mortality rates in childhood (1-5 years of age) and young adulthood (18-36 years of age), demonstrating that the sequelae of preterm birth extend beyond early infancy. Once a neonate at the extreme of viability has overcome the initial neonatal period, the root causes of the different types of preterm birth may play a greater role in post-neonatal mortality, for example growth restriction. In addition, post-neonatal exposures such as infections, and respiratory conditions may have a significant effect on mortality after this neonatal period. As such, physicians should be aware that the sequelae of preterm birth may continue beyond the period of neonatal intensive care and the causes of preterm birth may ‘program’ the subject for long term morbidities such as asthma, hypertension, or diabetes.

Preterm birth presents a major challenge in neonatal healthcare. Higher death rates occur in preterm infants, and preterm birth is an important risk factor for neurological impairment and disability. Over the last 30-40 years the incidence of preterm birth in most developed countries has been 5-7% of live births. Preterm birth not only affect the infants and their family, providing neonatal intensive care for preterm infants who might spend several months in hospital has increasing cost implications for health care providers, and long term health care for sequelae can also be expensive.

In Australia in 2009, 7.4% of babies born were preterm (less than 37 completed weeks of gestation). Of these 2487 babies were born at 20–27 weeks (0.8%), 2061 were born at 28–31 weeks (0.7%), and 17304 were born at 32–36 weeks (5.9%), Figure 15. The rate of preterm birth increased significantly over the last 2 decades, particularly for those <28 weeks’ gestation (Figure 15). Preterm birth and disorders relating to fetal growth accounted for 31.3% (837 deaths) of total 2009 perinatal deaths, similar in proportion to the 30.9% recorded in 2008.
Figure 15: Australian preterm births by gestational age, comparing 1991 and 2009. (74)

Figure 16: Australian low birth weight births by birth weight group, comparing 1991 and 2009. (74)

Preterm birth commonly follows spontaneous and unexplained preterm labour, or spontaneous preterm pre-labour rupture of the amniotic membranes. (70) Common causes of preterm births include preeclampsia, fetal distress, small-for-gestational age (intra-uterine growth restriction) and placental abruption. (71) Important predictors of spontaneous preterm birth include previous preterm birth, increasing maternal age, increased use of assisted reproductive technology and increasing rates of multiple births. (71) Possible explanations for higher rates of
prematurity with increasing maternal age may include co-morbid medical conditions related to age, such as diabetes, cardiovascular disease, hypertension and use of assisted reproductive techniques.(71) Higher rates of preterm birth in teenage mothers may result from lower socioeconomic factors and increased behavioural risk factors, such as cigarette smoking.(70,71) Intra-uterine infection was evident in approximately 70% of births before 28 weeks’ gestation, compared with only about 15% of births at 34-36 weeks’ gestation.(75) Delivering preterm babies is a balancing act contrasting the risks of preterm birth for the infant versus the consequences of continuing the pregnancy for the mother and fetus.(70)

Multiple birth increases the risk of preterm delivery.(70,76) In Australia, preterm birth occurred in approximately 57% of twins and in 95% of higher order multiple births, in comparison with approximately 7% of singleton births.(76) In Australia, in 2009 more births ≤28 weeks’ gestation came from twin and other multiple births (i.e. triplets, or higher) compared with singleton births.(76) In developed countries the incidence and survival of multiple pregnancies has increased over the past few decades.(76) The increase is mainly due to higher use of assisted reproduction techniques, for example, in vitro fertilisation.(76) In 2009, approximately 10% of women who had assisted reproduction and became pregnant had a multiple pregnancy.(76)

5.1.4 The preterm lung

Preterm birth happens during a vulnerable stage of lung development. Extremely preterm (EP, gestational age < 28 weeks) birth occurs when lung development is in the canalicular phase, when bronchioles, early capillaries, cilia and mucus glands in the bronchi form, whereas very preterm birth (VP, gestational age 28-32 weeks at birth) occurs during the saccular phase of lung development where saccules form from bronchioles, capillaries proliferate and surfactant production begins.(5,77) The later stages of lung development, after preterm birth, occur in the postnatal extraterine environment with adverse stimuli present, for example resuscitation, oxygen, mechanical ventilation, infection and inflammation.(5,77) The prenatal stage of life is an important time for development of the bronchial tree and alveoli, and it is now increasingly recognised that a significant proportion of respiratory symptoms and functional impairments in childhood and adulthood can be attributed to lung development during this pre and early postnatal phase. The clinical outcomes of preterm infants are determined by the circulatory and gas-exchange capacity of the lungs at birth, and also by treatments that are necessary for survival, which include but are not exclusive to oxygen therapy and mechanical ventilation. Preterm birth is associated with respiratory abnormalities throughout childhood, adolescence and early adulthood, including increased respiratory symptoms, decreased lung function and impairment of exercise performance: these outcomes will be discussed in more detail later.(71,78)
Respiratory morbidity and functional outcomes in infants born preterm is increasingly important as evidenced by the growing number of EP or ELBW infants, with the increase in numbers from 1991 to 2009 in Australia (Figure 15 and Figure 16).(76)

Lung development at 17-27 weeks’ gestation is in the late canalicular phase of development and transitions to the saccular stage at > 28 weeks. This coincides with the time of earliest extra uterine viability.(6) The extent of lung development during this time is substantial. By 32 weeks’ gestation, alveoli are present but are not true alveoli, which do not develop until the alveolar phase (36 weeks’ gestation).(79) Preterm birth interrupts the normal alveolar and vascular development, and gas exchange must occur earlier than otherwise intended.(77,79) Lung development following preterm birth continues in the extrauterine environment; this may result in disturbances in the development of the alveoli, pulmonary microvasculature and the gas exchanging regions of the lungs.(77,78) Under-nutrition (or growth restriction) and hypoxia in preterm infants may lead to disproportionate patterns of lung growth and development, which result in narrow airways in relation to lung size.(7) Subsequent failure of narrowed airways to catch-up, in terms of lung growth, may result in reduced expiratory flow through to adulthood.(7)

The two major determinants of lung development in preterm infants are the length of gestation and fetal growth.(1) Importantly there appears to be a significant relationship between lung development in utero and respiratory morbidity, and pulmonary function in later life.(1)

Respiratory function in preterm infants is affected by the immaturity of the lungs, delayed or impaired surfactant production, underdevelopment of the chest wall, and inability to effectively clear secretions.(77,78,80) These factors may cause pulmonary oedema, disruption of the blood-gas membranes, damage to the alveoli and inadequate gas exchange immediately after preterm birth.(77,80)

Preterm infants who do not develop lung disease in the newborn period have been shown to have abnormal lung function in comparison to healthy term-born babies, suggesting a disruption in acinar development or peripheral airways disease.(77,81) The lungs of a preterm infant face various challenges. Normal embryological development is interrupted by preterm birth; these processes were destined to follow a schedule of alveolar development and cellular maturation until term and beyond. They have immature lung structures that are highly vulnerable to epithelial injury.(82) The preterm lung is also biochemically deficient in a number of ways, with the most apparent the lack of metabolic capacity to produce, secrete and recycle pulmonary surfactant.(82) Add to that low elastic recoil provided by the rib cage and compliant airways, and the result is a respiratory system that is not well equipped for the extra-uterine environment.(77,82) The reductions in lung function in these preterm infants without lung disease
may be due to premature exposure of immature alveoli to breathing air, and to the mechanical forces involved in the act of breathing.(77,81)

5.1.4.1 Gestational age versus birth weight

There is often incomplete recording and uncertainty around estimates of gestation.(70) In Australia, data on birth weight and gestational age are routinely collected.(76,83) Although there are some similarities between the categories of birth weight and gestational age, they are not interchangeable.(70) The following are categories for birth weight:

- Normal birth weight – birth weight $\geq$ 2500 g (NBW)
- Low birth weight – birth weight < 2500 g (LBW)
- Very low birth weight – birth weight <1500 g (VLBW)
- Extremely low birth weight – birth weight < 1000 g (ELBW)

Not all low birth weight infants are born preterm.(70) Term infants may have low birth weight because they are “small for gestational age (SGA)” or “light for dates”.(70) These infants are usually described as being below the 10th centile for birth weight by gestation, or more than 2 SDs below the mean when compared with expected ranges.(70) Preterm babies may also be small for gestation.(70) The may have issues other than just having a short gestation, such as intrauterine growth restriction.(70) Intrauterine growth restriction or being born SGA are risk factors for respiratory morbidity in childhood. Most literature surrounding lung function outcomes after intrauterine growth restriction has arisen from studies using animal models. For example, Chen et al demonstrated structural lung changes in rats that were exposed to late gestation maternal malnutrition including lower alveolar numbers and increased septal thickness.(84) In another animal study looking at fetal sheep following maternal malnutrition the lambs had reduced lung weight and volume, reduced alveolar surface areas, reduced pulmonary diffusing capacity and lung compliance and marked chest wall stiffness.(85,86) Greenough et al reported increased rates of wheezing, respiratory tract infections and lung function abnormalities in children who were SGA at birth, such as higher airways resistance in SGA preterm children compared with NBW controls.(87) Rona et al. reported a significant correlation between lung function and birth weight (adjusted for gestational age) in 5 to 11 year old children, suggesting that reduced birth weight for gestational age is associated with worse lung function outcomes at school age.(88) In addition, reduced airway function (FEV$_1$ and FVC) has been reported in adults born with lower birth weights by Barker et al.(89) Historically chronic intrauterine stress, leading to intrauterine growth restriction and infants born SGA, has been thought to accelerate pulmonary maturation compared to infants born with weights appropriate for gestational age.(90-92) More recently this theory has been
challenged with many studies showing increased risks of adverse outcome, such as, asphyxia events, respiratory distress syndrome, respiratory failure and increased mortality compared to appropriate for gestation infants. The associations that may or may not exist between intrauterine growth restriction leading to SGA infants and lung function outcomes is complicated by the lack of discrimination between SGA and prematurity, both of which have been shown to affect respiratory function, but perhaps in different ways. Confusion also arises from using low birth weight, which refers to infants with birth weights <2500 g as a substitute for IUGR or SGA infants. The term low birth weight refers to infants’ birth weights and is not adjusted for gestational age; most low birth weight infants have appropriate growth for their gestation.

It should also be noted that lower birth weight have been associated with a lower amount of lean mass and muscular strength, these may affect the muscles involved with effective ventilation.

In Australia, 6.2% of live births were babies of low birth weight. From 1991 to 2009, the rate ranged from 6.2% to 6.8%. VLBW babies made up 0.6% and ELBW made up 0.5% of all live births in Australia in 2009 (Figure 16). Many VLBW infants now survive through to adulthood because of improvements in neonatal care.

Broadly speaking, outcomes after preterm birth improve as gestational age increases, but this relationship is linked to birth weight.

5.1.4.2 Mechanical ventilation

In the late 1970s and early 1980s, treatment of respiratory compromise after preterm birth was supportive and consisted of mechanical ventilation and high inspired oxygen (O₂) concentrations. Taghizadeh et al., in 1976, suggested the use of high peak airway pressure during mechanical ventilation was an important component in the pathogenesis of BPD. Respiratory symptoms in the early years of life have been shown to be associated with the duration of mechanical ventilation in survivors of hyaline membrane disease (HMD). The term ventilator-related lung injury historically was described leakage of air from the disrupted airspace wall. Recently Attar et al. recognised that mechanical ventilation may cause more subtle physiologic and morphologic alterations within the lungs, such as higher incidences of wheezing, ‘asthma-like’ symptoms, hyper-reactivity of their airways and increased levels of inflammatory markers.

Infants are vulnerable to respiratory failure due to a number of features in their developmental physiology, such as high metabolic rates relative to their size, decreased lung compliance, high chest wall compliance, decreased FRC, and increased airway resistance.
Mechanical ventilation of lungs where a large number of airspaces are open allows the delivered tidal volume to be distributed widely and evenly. If a lung is diseased, e.g. neonates with BPD, the tidal volume during mechanical ventilation may be delivered to regions within the lungs that are open and not to areas that are atelectatic; this may lead to over-ventilation of the open regions of lung.(82) Mechanical ventilation can worsen acute lung disease.(95) The mechanical damage can cause fluid, protein and blood to ‘leak’ into the airways, the alveoli and the lung parenchyma, inhibiting surfactant production and promoting lung inflammation.(95) Positive pressure mechanical ventilation can lead to maldistribution of tidal volume where some areas receive a high volume and some areas are not ventilated.(82) The method of mechanical ventilation can have significant effects on severity and distribution of lung injury.(82) This can lead to substantial disruption to the lining of the airspaces, in particular the terminal bronchioles in the acinar lung zone.(82) ‘Ballooning’ and ultimately rupture of the developing bronchioles is a common response to ventilation and leads to interstitial emphysema and the beginnings of the inflammatory response.(82)

Volutrauma and barotrauma from mechanical ventilation are key factors in the development of BPD.(96) Animal studies have demonstrated that long periods of ventilation disrupted lung development and resulted in histopathologic pulmonary changes that were very similar to those seen in the preterm infants who had died with BPD.(4) Hayes et al. ventilated preterm lambs for an extended period and reported uneven ventilation patterns, impairment in alveolar formation, increases in elastin deposition, and muscularisation of terminal bronchioles, with inflammation and oedema also present.(4) Atta et al. reported interstitial and alveolar oedema following mechanical ventilation using high pressures.(95) Attar et al. stated that “severity of these microscopic alterations was unevenly distributed”.(95) Toews et al. describe the fibroproliferative response after an initial lung injury as an attempt to repair damage done to the blood-gas barrier during mechanical ventilation, and that the response was apparent within a few hours.(97) Toews et al. and Attar et al. describe effective repair of the blood-gas barrier and the interstitium involving:

- intra-alveolar debris removal;
- fibroblast recruitment, proliferation, and differentiation to restore of the extracellular matrix;
- alveolar surface re-epithelisation; and
- new capillary formation.(95,97).

Airway pressures are monitored during mechanical ventilation whereas trans-pulmonary (alveolar – pleural pressure) pressures are not and may be more relevant.(95) Dreyfuss et al. showed, in a ventilated rat model, that high pressures during ventilation with low volumes did not
increase pulmonary oedema, and that lung volume was the important factor in inducing oedema, not ventilation pressure. In preterm infants with respiratory distress the lung volume functional residual capacity (FRC) and total lung capacity (TLC) may be low. This leaves little room to avoid high and low lung volume injury areas. If ventilation is not evenly distributed this may lead to the ventilated portion of the lung being over-ventilated and volutrauma.

The Australian and New Zealand Neonatal Network (ANZNN) collect data from level III neonatal intensive care units and level II special care units across Australia and New Zealand. The data are from neonates within these departments who were born <32 weeks’ gestation or who weighed <1500 g or who received mechanical ventilation, or those neonates who died while receiving mechanical ventilation, or underwent major surgery or finally, those who received therapeutic hypothermia treatment. Therefore, this is a specially selected group of high-risk neonates and does not represent all neonates. The ANZNN published their most recent report in 2009. They found mechanical ventilation was most commonly used in infants with hyaline membrane disease (HMD, 62.5%), which is caused by surfactant deficiency.

A delicate balance must be struck when choosing an appropriate level of mechanical ventilation in order to maintain adequate lung expansion but avoid over-distension in neonates with vulnerable lungs who have minimal RDS in order to reduce the amount of barotrauma and volutrauma neonates are exposed to, this in turn may reduce the numbers on neonates who go on to develop BPD.

5.1.4.2.1 Type of mechanical ventilation

Mechanical ventilation utilises a significant component of the resources available in a neonatal care setting, and requires specialist nursing techniques and medical intervention. The ANZNN states in 2009 that the 2 major types of mechanical ventilation used are continuous positive airways pressure (CPAP) and intermittent positive pressure ventilation (IPPV). IPPV is assisted ventilation administered by endotracheal tube and CPAP can be given endotracheal tube, or much more commonly via nasopharyngeal prongs (nasal CPAP).

In 2009, babies in the ANZNN database received a median of 9.9 days of mechanical ventilation; the number of days was inversely proportional to gestational age. The most common form being CPAP (44.2% ANZNN registrants) followed by IPPV (14.7% ANZNN registrants). In addition to CPAP and IPPV, infants may receive supplemental O₂ (sometimes via high-flow nasal cannula), high frequency oscillatory ventilation (HFOV), nitric oxide (NO), and/or extracorporeal membrane oxygenation (ECMO).
It is important to remember that every type of assisted ventilation may be a ‘second insult’ to the lung and could amplify any injury and subsequent inflammatory response. (4)

In preterm infants with respiratory distress but sufficient spontaneous breathing non-invasive ventilation may provide sufficient assistance, where an infant is not sufficiently ventilating more invasive ventilation with intubation and mechanical ventilation may be the only alternative. There have over the past few decades been advances in types and modes of mechanical ventilation, some of which are technologically complex. There are 2 main types invasive mechanical ventilation: conventional ventilation and high frequency ventilation. Conventional ventilation is based on tidal volume and how each breath in started and finished. High frequency ventilation uses smaller tidal volumes and very fast rates to try to overcome large volume swings seen with conventional ventilation.

With the advances over the past decades in neonatal care have come changes in the mechanical ventilation strategies used in preterm/ELBW survivors, such as non-invasive ventilation in an attempt to reduce trauma caused to the vulnerable lungs of preterm infants. (99) CPAP is commonly used in neonatal units worldwide as a primary form of respiratory support and continuing respiratory support following extubation from mechanical ventilation. (99) CPAP provides positive pressure that increases FRC and therefore improves oxygenation, reduces airway resistance, work of breathing and helps diaphragmatic functioning. (99)

With the advances in the technology that surrounds transducers and signal processing power researchers have been able to measure spontaneous breathing efforts in neonates and develop ventilators that respond to these inputs.

5.1.4.3 Oxygen therapy

Supplemental O₂ therapy is the most common treatment used in the care of preterm babies. O₂ supplementation may be critical for survival in some preterm infants, especially those who suffer respiratory distress. The duration and concentration of supplemental O₂ can vary from just a few hours or days, to several weeks or months. Babies born preterm are very sensitive to the harmful biochemical effects of O₂. Exposure to high O₂ concentration may cause direct oxidative damage by increasing the production of reactive oxygen species; these are increased in high oxygen environments and in re-oxygenation after hypoxia. (4,100) EP and ELBW infants may be particularly susceptible to hyperoxia and reactive oxygen species damage because their antioxidant system is immature, and lacks plasma radical scavengers e.g. beta-carotene, and antioxidant enzymes e.g. glutathione peroxidase. (4,100) Protracted mechanical ventilation and O₂ supplementation may cause irreversible lung damage. Exposure to oxygen therapy has the potential to cause oxidative lung injury involving both the conductive airways and acinar lung
High levels of oxygen may constrict or destroy the blood vessels in immature eyes and brains, causing injury. The harmful effects of O\textsubscript{2} may play a major role in the pathogenesis of chronic lung disease as well as other systemic diseases, e.g. retinopathy of prematurity (ROP), intraventricular haemorrhage (IVH), or necrotising enterocolitis (NEC), which means there is a balance required between O\textsubscript{2} toxicity and O\textsubscript{2} supplementation. Published studies have demonstrated that high O\textsubscript{2} concentrations may cause major effects on lung tissue, such as epithelial type II cell and fibroblast proliferation, changes to surfactant production, increased levels of cytokines and inflammatory cells, increased collagen deposition, and reduced alveolarisation and vascular complexity. Conversely there is also concern that low O\textsubscript{2} concentration may lead to reduced growth and poor neurosensory outcomes. Duelofeut et al. reported data that support targeting oxygen saturations in the range 85-93%, rather than >92% and found a decrease in the incidence of ROP, oxygen use at 36 weeks, and use of steroids for chronic lung disease, without increased levels of NEC, IVH or periventricular leukomalacia (PVL), or a detrimental effect on developmental outcome at 18 months’ corrected age.

In the 1950s it was proven that high O\textsubscript{2} concentrations were a major cause of ROP. The supplemental therapeutic oxygen for pre-threshold retinopathy prematurity (STOP ROP) trial used pulse oximetry to target lower levels (89-94%) or higher levels of oxygen saturation (≥ 95%) in 649 preterm infants from 30 centres. Those infants in the higher range (n=324) had more adverse respiratory events, such as pneumonia, bronchopulmonary dysplasia (BPD) requiring oxygen therapy and diuretics, and hospital admissions at 3 months’ corrected age. Lower inspired oxygen (targeting oxygen saturations less than 90%) may increase patent ductus arteriosus (PDA), pulmonary vascular resistance and chronic lung disease. Whereas more inspired oxygen (targeting oxygen saturations greater than 90%) may increase severe ROP and chronic lung disease. The question arises whether these pathologic changes in early life contribute to diminished lung function and exercise capacity in later life.

In 2005 the ANZNN reported that 49% of infants <28 weeks’ gestation had ROP, and 12.4% had RP considered severe (Grade III or IV). So, ROP is still a major ongoing problem, despite the ability to monitor oxygen saturation continuously.

### 5.1.4.4 Hyaline membrane disease (HMD) and respiratory distress syndrome (RDS)

Signs of respiratory distress in infants shortly after birth include increased work of breathing characterised by intercostal and sub-coastal recession, nasal flaring, and expiratory grunting where the infant is attempting to maintain their FRC by partially closing the glottis, increased respiratory rate (>60 breaths.min\textsuperscript{-1}) and cyanosis. The chest x-ray shows atelectasis and a diffuse ground glass appearance. If an infant displaying these features is left untreated, the
condition will worsen over 48-72 hours, before improving as surfactant is produced endogenously, provided the baby survives. RDS in preterm infants is caused by immaturity of the structure within the lungs and insufficient production of surfactant. Nowadays with early use of surfactant and IPPV, the classical signs of RDS are uncommon. Because preterm infants commonly have respiratory complications and they may be ventilator- or O2-dependent for extended periods they may develop chronic lung disease of infancy, which is now generally termed BPD. Alveolar epithelial cell necrosis is an early histological finding in RDS. Epithelial cells detach from the basement membrane and hyaline membranes form on the exposed areas. Hyaline membranes form when plasma proteins leak onto the lung surface through damaged capillaries and epithelial cells and coagulate. They are “waxy-appearing layers of hyaline membrane” lining air spaces that have collapsed in the lung (Figure 17). Mechanical ventilation and O2 therapy, while critical for survival, may also damage the lung. RDS is now the common term used as hyaline membrane disease strictly requires histological confirmation, which rarely happens due to the low number of deaths of infants with RDS.

Figure 17: Hyaline membranes in a neonate with RDS (adapted from (67))

The incidence of RDS increases with decreasing gestational age. RDS begins soon after birth and symptoms are described above. RDS resulting from pulmonary surfactant deficiency has been responsible for a high proportion of EP and ELBW infant deaths and much of the resultant respiratory morbidity.(82) As the RDS progresses, the infant may develop ventilatory failure, and prolonged cessation of breathing (apnoea).(82) Despite advances in neonatal care, RDS is still the most common cause of death in EP neonates. Complications related to RDS include metabolic disorders, patent ductus arteriosus (PDA), low blood pressure, chronic lung changes, and intracranial haemorrhage.(82,105) Prematurity further complicates RDS as it may add additional defects in other organ functions.(105) EP infants frequently have BPD as a complication of neonatal care for RDS, resulting in high incidences of BPD in the most immature survivors.(105)
5.1.4.5 Pulmonary surfactant deficiency

Pulmonary surfactant is a complex of lipids and proteins that lines the air-liquid interface at the alveolar epithelial surface and stabilises it during respiration. Surfactant is produced in special cells in the lungs called alveolar type II epithelial cells and it assists in rapid oxygen perfusion from the alveoli to the pulmonary capillaries. Pulmonary surfactant prevents collapse of the alveoli by reducing the surface tension across the blood-gas interface of the alveoli. Surfactant deficiency causes a disturbance in gas exchange by creating a ventilation/perfusion mismatch. This can be seen in preterm infants with RDS. Pulmonary surfactant also has a role in several defence mechanisms in the lung. In small airways, pulmonary surfactant helps maintain patency. The surfactant complex consists mostly of lipids and some protein, including four surfactant proteins (SP-A, SP-B, SP-C and SP-D).

The most abundant surfactant protein, SP-A, was first identified by King et al. SP-A and SP-D are structurally related hydrophilic collagenous glycoproteins. SP-B and SP-C are small hydrophobic proteins that help facilitate the spreading and stability of the surfactant film at the blood-gas barrier. SP-B is required for the normal processing of the surfactant components in type II epithelial cells, and SP-C is protein that contributes to the formation and maintenance of the surface-active monolayer. SP-A and SP-D participate in pulmonary surfactant homeostasis and host defence. The protein involved in bacterial and viral clearance is SP-A. SP-A, SP-B and SP-D are seen in alveolar type II epithelial cells and bronchiolar epithelial (Clara) cells, whereas SP-C is detected only in alveolar type II epithelial cells.

Since the early 1990s exogenous surfactant has become widely available in Victoria, having been first used in March 1991 at the Royal Women’s Hospital in Melbourne. The 1991-1992 cohort of EP or ELBW survivors born in the state of Victoria that forms the basis for this thesis is unique, as they are one of the first regional cohorts born in the surfactant era. In 1991 exogenous surfactant was used as a rescue therapy, but only in babies with lung disease who required ventilation and at least 50% oxygen. In 1992 surfactant was used more readily in preterm babies, but still as rescue therapy, rather than being given prophylactically to all babies born below a certain gestational age or birth weight. The effect of surfactant on the development of BPD, chronic lung disease of infancy, has been reported by many authors, with differing outcomes. This is due to different methods employed in the studies with limitations including small sample sizes, low follow-up rates and inappropriate baseline reference data. The 1991-1992 cohort includes 38.3% of individuals treated with surfactant, but they tended to be of lower gestational age. There was no significant difference found in the lung...
function at 8 years of age of those in the 1991-92 cohort who were treated with surfactant and those who were not. (91)

The surfactants available currently are either animal-derived (‘natural’) or synthetic. (96) The original synthetic surfactants contained phospholipids but lacked surfactant proteins present in the natural surfactants. (96) Soll et al. reported the use of natural surfactant versus synthetic surfactant has led to greater improvement in initial ventilator requirements, lower rates of pneumothorax and a trend towards increased survival. (113) Soll et al. also reported that natural surfactant may be associated with an increase in intraventricular haemorrhage, although they reported the more serious haemorrhages (Grade III and IV) were not increased. (113) Postnatal surfactant administration given either as prophylaxis or treatment (i.e., to infants with established RDS) reduces mortality and the incidence of pneumothorax compared with that seen in the no surfactant groups. Prophylactic surfactant administration to infants judged to be at high risk of RDS (infants <30-32 weeks of gestation) compared with selective use (that is in infants with established RDS), however, may be more efficacious. Meta-analysis of the results of eight randomised trials demonstrated that prophylactic administration was associated with decreased risks of pneumothorax, pulmonary interstitial emphysema and mortality. (113) Similarly, early selective administration (surfactant administration to infants intubated for RDS and given within the first 2 h after birth) compared with delayed selective administration to infants with established RDS, improves outcome. (114) Meta-analysis of the results of four randomised trials demonstrated that early selective administration was also associated with decreased risks of pneumothorax, pulmonary interstitial emphysema and mortality. (114) In infants with established RDS, multiple doses rather than a single dose of surfactant result in greater improvements in oxygenation and ventilatory requirements, and a decrease in pneumothorax, with a trend towards improved survival. (115)

The surfactant is stored by the cell in structures called lamellar bodies, and delivered into the air-spaces. (4) The lamellar bodies then unfold into a phospholipid monolayer that lines the air-liquid interface. (4) This layer reduces the surface tension of the air-space. (4) Surface tension within the lungs is responsible for a significant amount of the elastic recoil forces of the lungs. (4) By reducing surface tension, surfactant stops the air-spaces from completely collapsing during exhalation. (4) Also, the decreased surface tension means that re-opening of the air space requires a lower amount of force. (4) Therefore, when there is a surfactant deficiency, the air spaces collapse and are difficult to expand. (4) Microscopically, a surfactant deficient lung has collapsed air spaces alternating with hyper-expanded areas, vascular congestion and, eventually, hyaline membranes will form if the infant lives long enough. (4) Effective surfactant must be able to change its properties during the breathing cycle: it must have a very high surface tension at the
beginning of expiration to allow oxygen diffusion, and then surfactant surface tension must
decrease at the end of expiration to prevent alveolar collapse.

Surfactant develops relatively late in gestation. The lungs of preterm neonates with RDS
are developmentally deficient in surfactant.(4) Exogenous surfactant administered to babies with
moderate to severe HMD has been shown to reduce the severity of the disease and the
mechanical ventilation requirements.(104) For babies born at less than 31 weeks’ gestation most
benefit is gained by early administration of exogenous surfactant (within two hours of birth).(104)
For babies born at 31 or more weeks’ gestation exogenous surfactant is usually only administered
to those with a confirmed diagnosis of RDS.(104)

Surfactant deficiencies have been reported in infants with BPD. Sobel et al. described that
some ELBW infants had respiratory deterioration with the need for mechanical ventilation and
oxygen around 10 days post-surfactant.(116) Merril et al. showed that 75% of mechanically
ventilated preterm infants had dysfunctional surfactant and a deficiency in SP-B and SP-C.(117)
Lungs of preterm infants with surfactant deficiency may be injured with the initiation and
continued use of mechanical ventilation.

5.1.4.6 Glucocorticosteroids

Currently, antenatal corticosteroids are effective in reducing the incidence of RDS.(75)
Liggins et al. in 1972 reported that corticosteroid exposure in preterm fetal sheep led to
maturational process within the lungs of the sheep.(118) This was an important step in the
evolution of management of preterm delivery.(75) Glucocorticosteroids are used antenatally to
accelerate lung maturation, and postnatally in preterm infants on mechanical ventilation to
improve their respiratory condition and reduce inflammation, but the effect of postnatal
corticosteroids on growth and development in these infants causes concern.(95,119-121)
Inflammation is thought to play an important role in the pathogenesis of chronic lung disease in
infancy.

Randomised controlled trials have shown corticosteroids given to mothers who may
deliver preterm is one of the few interventions known to improve short-term outcome for the
preterm infant.(122) Corticosteroids are known for many years to have powerful biological
effects, some of which could be harmful.(122) In humans, outcomes in early childhood survivors
from the randomised trials have been encouraging, and no major deleterious effects have been
reported.(122) However, it is possible that detrimental effects will still occur in later life, even into
adulthood.(122)
The widespread introduction of antenatal corticosteroids is an important change in perinatal practice.(123) Antenatal corticosteroids improve the outcome of prematurely born infants particularly reducing the incidence of RDS and improved survival. Early data on the use of systemic corticosteroids was promising for preventing chronic lung disease. Roberts et al. reported results of a meta-analysis including 21 randomised studies and demonstrated that antenatal administration of dexamethasone or betamethasone to pregnant women reduced the incidences of RDS (OR: 0.66; 95% CI: 0.59-0.73), neonatal death (OR: 0.69; 95% CI: 0.58-0.81), cerebral haemorrhage (OR: 0.54; 95% CI: 0.43-0.69) and necrotizing enterocolitis (OR: 0.46; 95% CI: 0.29-0.74).(124)

There is concern over the use of systemic corticosteroids after birth leading to worse neurosensory outcomes.(96,121) Halliday et al. found infants receiving postnatal systemic steroids had a higher incidence of cerebral palsy, developmental delay and abnormal neurodevelopmental outcomes.(121). It may be difficult in the studies to differentiate whether adverse events relate to the use of postnatal corticosteroids per se or whether introduction of postnatal corticosteroids has led to increased survival and therefore increased incidence of these adverse events, a survivor effect. Postnatal corticosteroids are used as they may assist with weaning from mechanical ventilation and reduce the durations required for supplemental oxygen. Gross et al. reported no differences in lung function, neurological and cognitive outcomes from a small study in the 1980s between 15 year old who had received prolonged courses of dexamethasone when compared with control, although those with less exposure to dexamethasone had lower lung function.(125) Nixon et al. reported similar findings in lung function in children aged 8-11 years following postnatal dexamethasone.(126)

5.1.4.7 Bronchopulmonary dysplasia – a changing picture

The phrase “Chronic Lung Disease” in infancy covers a heterogeneous group of diseases that usually evolves from an acute newborn pulmonary disorder. These disorders, such as respiratory distress syndrome (RDS), meconium aspiration, sepsis, persistent pulmonary hypertension, and congenital heart disease require interventions that may lead to the development of BPD. BPD is a complex disorder with multiple factors contributing to its onset and progression.(4)

To understand BPD in this era, an historical perspective is useful.(127) The term BPD was coined in the 1960s by Northway et al. to describe lung damage that occurred in infants with respiratory failure with characteristic chest x-ray changes who were mechanically ventilated (128) Dysplasia indicated the impaired development that occurred after damage and trauma to the vulnerable immature lungs. The lung damage in the infants was attributed to the use of aggressive
mechanical ventilation and high inspired oxygen concentrations. The repeated opening and closing of alveoli (atelectrauma) at high pressures (barotrauma) and high volumes (volutrauma) in the context of high concentrations of oxygen (chemotrauma) caused cystic and fibrotic changes in the lung. Coupled with increased risks of infection and inflammation (biotrauma), this led to the development of BPD. BPD is defined as infants who are chronically oxygen dependent. The definition has evolved over time and includes various criteria, including oxygen dependency beyond 28 days postnatal days and oxygen dependency at 36 weeks’ postmenstrual age. Recently the National Institutes of Child Health and Human Development (NICHD) workshop published diagnostic criteria for BPD that include disease severity and gestational age (Table 2). The NICHD also recommended that the original nomenclature of BPD be used instead of chronic lung disease of infancy to save confusion with adult diseases, such as chronic obstructive pulmonary disease. The definition of BPD is useful for epidemiological studies as it is simple, but it does not provide information on the pathology, disease progression or variability of the lung pathology.

Table 1: Definition of BPD – Diagnostic criteria

<table>
<thead>
<tr>
<th>Gestational age</th>
<th>&lt;32 weeks</th>
<th>≥32 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild BPD</strong></td>
<td>Breathing room air at 36 weeks’ PMA or discharge, whichever comes first</td>
<td>Breathing room air by 56 days’ postnatal age or discharge, whichever comes first</td>
</tr>
<tr>
<td><strong>Moderate BPD</strong></td>
<td>Need* for &lt;30% oxygen at 36 weeks’ PMA or discharge, whichever comes first</td>
<td>Need* for &lt;30% oxygen at 56 days postnatal age or discharge, whichever comes first</td>
</tr>
<tr>
<td><strong>Severe BPD</strong></td>
<td>Need* for ≥30% oxygen and/or positive pressure (PPV or nCPAP) at 36 weeks’ PMA or discharge, whichever comes first</td>
<td>Need* for ≥30% oxygen and/or positive pressure (PPV or nCPAP) at 56 days’ postnatal age or discharge, whichever comes first</td>
</tr>
</tbody>
</table>

Definition of abbreviations: BPD bronchopulmonary dysplasia; NCPAP nasal continuous positive airway pressure; PMA postmenstrual age; PPV positive-pressure ventilation. * A physiologic test confirming that the oxygen requirement at the assessment time point remains to be defined. This assessment may include a pulse oximetry saturation range.

Older BPD or “classical” BPD was diagnosed in infants who often had severe respiratory failure in the neonatal period with pulmonary fibrosis and airway smooth muscle hypertrophy. Oxygen toxicity was originally blamed as the cause of BPD and continues to be a major factor today. The preterm infants who Northway et al. described as having BPD were born in a later phase of lung development and with severe respiratory symptoms and characteristic chest x-ray changes and therefore did not offer much diagnostic difficulty. Their lung development was well into the late saccular and early alveolar phase when the first alveoli are developed. In the era before the routine use of antenatal glucocorticosteroids and post-natal exogenous surfactant, pathologic examination of infants who died of BPD showed...
chronic fibrotic changes, with areas of interstitial emphysema which frequently combined into large cystic regions, surrounded by airway collapse.(133)

Newer BPD can be defined in infants who become chronically oxygen dependent despite minimal or no initial respiratory distress.(133) Exposure to mechanical ventilation and oxygen are further complicated in preterm neonates who have an immature or deficient pulmonary antioxidant defence system, which may lead to inability to resist and repair ongoing injury.(36) The use of pulmonary surfactant has been important in changing the face of ‘older’ BPD.

BPD remains a major adverse outcome of neonatal intensive care, now primarily observed in EP infants weighing less than 1000 g and born at 24-28 weeks’ gestation.(133) Despite the advances in the intensive care provided to EP or ELBW infants in the modern era, the fact remains a small proportion will develop respiratory failure, and many will go on to develop BPD with an ongoing requirement for oxygen at and beyond 36 weeks’ corrected gestational age. These infants may even require supplementary oxygen at home.(133) Prolonged periods of high oxygen concentrations and mechanical ventilation lead to biochemical and histological effects on lung tissue.(4) BPD is a common chronic lung disease affecting EP and ELBW infants.(81) The infants have chronic hypoxemia and often need mechanical ventilation for extended periods of time. The lungs of these infants with BPD now tend to have less fibrosis and more uniform inflation than in the past.(75) However they have simplified gas exchange structures with fewer larger alveoli, indicating disruption with alveolarisation in the developing lung.(75,134) Severe cases of BPD are also associated with clinical pulmonary hypertension and abnormal pulmonary vascular development. Subclinical pulmonary hypertension is also associated with milder cases of BPD.(134) The development of BPD is now widely viewed as a consequence of lung inflammation, potentially arising from the exposure to intrauterine infection, inflammation (such as chorioamnionitis) before birth and mechanical ventilation and supplemental oxygen after birth.(5,75,78,135-137)

With the use of better ventilation techniques for infants, survival increased for the larger preterm infants born in the late 1970s but more survivors developed BPD.(127) The association of volutrauma and barotrauma with BPD has led to the use of ventilation strategies such as permissive hypercapnoea to keep the lung injury to a minimum. Although there has been no ideal ventilation mode found so far, it is clear that tidal volumes and inspired oxygen levels should be kept to a minimum to avoid hypocarbia, volutrauma or oxygen toxicity. Alternative strategies, such as using nasal CPAP to avoid intubation and mechanical ventilation have been used more recently.(99,138,139) After the early 1990s surfactant treatments and the general use of antenatal corticosteroids, survival of the ELBW infant increased further.(127,140) Autopsy specimens from subjects who had BPD from the 1990s have shown airway wall thickening.(141,142) It is also apparent that treatments necessary for survival in these infants,
such as mechanical ventilation, antenatal corticosteroids, oxygen and surfactant therapies may further affect the normal alveolar and pulmonary vascular development. Abnormalities of gene expression for inflammatory regulation, surfactant synthesis and vascular development may play a role in new BPD development. The rates of BPD have increased alongside the improved survival of smaller and more immature infants, BPD is a major predictor for adverse outcomes, including poor neurodevelopmental, with increased rates of cerebral palsy and other motor abnormalities, poor cognitive outcomes during early childhood and school-age, and impaired long term respiratory function and exercise capacity. In addition, chronic health issues associated with BPD have a major effect on the daily life of families that continues beyond the newborn period, after the child goes home.

With the shift in the population to infants with lower gestational age and birth weight, pathological reports of ‘new’ BPD show infants have little to no injury, have less inflammation and fibrosis, but have simplified airspaces typical of delayed or interrupted development of the acinar lung zone with abnormal alveolarisation of the lungs, and disrupted vascularisation (Figure 18).

Figure 18: Lung histology. (A) Early control lung showing large-sized, simple airspaces, relatively wide septa, and focal early secondary crest formation (asterisks), characteristic of late canalicular/early saccular stage of lung development (infant born at 24 weeks’ gestation; lived for 2 h). (B) Short-term ventilated lung showing widening and increased cellularity of the septa, as well as focal haemorrhages within the air spaces (infant born at 23 weeks; lived for 7 d, ventilated). (C) Late control lung showing complex gas-exchanging parenchyma with abundant secondary crests (asterisks) and thin alveolar septa, consistent with late saccular/early alveolar stage of lung development (stillborn at 38 weeks). (D) Long-term ventilated lung showing simple, large-sized air spaces with hyper-cellular and thickened septa (infant born at 27 weeks, lived for 12 weeks, ventilated).

Similarly preterm baboons and lambs exposed to mechanical ventilation and oxygen therapy have major lung abnormalities, such as dilated alveolar ducts, reduced alveolarisation and
decreased gas exchange surface area. (133) Abnormal pulmonary vascular development and decreased or disrupted alveolarisation are hallmarks of the newer BPD. (96) It has been shown that inhibition of vascular growth impairs alveolarisation. (148) Alveolar arrest has been used to describe the radiological findings within new BPD. The term ‘arrest’ usually means to render inactive. Its use in describing BPD may be misleading, meaning that sustained or permanent cessation of alveolarisation might be presumed, rather than an interruption. The EP or ELBW infants who comprise those at risk for the newer BPD are born in the late canalicular and early saccular phases of lung development, between 24 and 28 weeks of postmenstrual age. (149) During this period the developing lung undergoes significant alteration of both the pulmonary epithelium, which develops from the terminal bronchioles to form canaliculi and the acini, and the surrounding mesenchyme, which supports the growth of capillaries surrounding the airways. The nature and relative roles these factors play with immaturity to induce BPD in the EP or ELBW infant are unknown, although some insults such as volutrauma, hyperoxia and inflammation, cause injuries similar to BPD in animal models. (81)

There is mounting evidence that BPD may result from an imbalance of pro-inflammatory and anti-inflammatory mechanisms. (4) The inflammatory response includes a rapid accumulation of neutrophils and macrophages in the airways and lung tissue of mechanically ventilated preterm infants and may affect the alveolar-capillary unit and tissue integrity. (4)

Infections, such as with Ureaplasma spp. and chorioamnionitis caused by other organisms are significant risk factors for the development of RDS that may develop into BPD. (4) Viscardi et al. showed the preterm infants less than 1500 g with Ureaplasma urealyticum infection of the lower respiratory tract were two times as likely to have BPD or to die compared with non-infected infants who were of similar birth weight. (150) Abele-Horn et al. demonstrated that Ureaplasma urealyticum infection was a risk factor for the development of BPD in surfactant treated preterm infants. (151) Bhandari et al. confirmed that the presence of Mycoplasma in tracheal aspirates in preterm infants was correlated with a significant risk of developing severe BPD. (4,152) In addition to postnatal infection, antenatal chorioamnionitis has been speculated as a contributing factor for BPD. (4) Watterberg et al. demonstrated that low birth weight infants who developed BPD had an increased exposure to chorioamnionitis with subsequent prenatal inflammation and evidence of increased inflammation in the lung. (4,135) Kramer et al. showed that severe lung inflammation occurred in mechanically ventilated preterm lambs. Also, Young et al. reported that preterm infants exposed to chorioamnionitis have increased rates of tracheal colonisation, which might predispose them to developing BPD, with an odds ratio of 2.42 (p<0.05). (4,153) Preterm infants with various severities of BPD have higher and more persistent numbers of inflammatory cells in their bronchoalveolar lavage (BAL) compared with infants who recovered from RDS. (4) Cytomegalovirus (CMV), acquired after birth, may also play a role. Sawyer et al. found x-ray
evidence that BPD occurred in 75% of preterm infants infected with CMV postnatally compared with approximately 40% in age-matched non-infected NBW control. (4,154)

Antenatal and postnatal factors, such as mechanical ventilation or oxygen therapy, contribute to the release of pro-inflammatory and anti-inflammatory cytokines. (134) Cytokines are proteins that interact with cells of the immune system in order to regulate the body’s response to disease and infection. Cytokines (e.g. Interleukin-1, Interleukin-6, and Interleukin-8) are synthesised by various inflammatory and pulmonary cells upon stimulation by hyperoxia, bacteria and physical factors such as barotrauma and volutrauma. (4) Chorioamnionitis and postnatal infections may increase the inflammatory response of the preterm lung to mechanical ventilation and oxygen exposure; this may reflect an inability to regulate inflammation. (4) An imbalance in these cytokine mediators leads to activation of the cellular death pathways within the lung; this may be followed by healing (a resolution of injury to normal lung architecture) or repair. (134) This repair is characterised by impaired alveolarisation and pulmonary vasculature. (134)

With the introduction of antenatal glucocorticosteroids and exogenous surfactant, the impact of surfactant deficiency has been significantly lessened. (82) This will have major implications for the application of mechanical ventilation and oxygen therapy, in terms of the volume of lung that is accessible and the subsequent potential exposure of the immature epithelium to increased oxygen level and volutrauma. (82) Husain et al. reported on 14 surfactant-treated infants with BPD, 8 non-surfactant-treated BPD subjects and 15 age matched controls from 1988 through to 1994. (155) The infants were treated with 3 doses of exogenous surfactant (either Exosurf™ or Survanta™) during the first 24 hours. (155) The gestational ages of the surfactant BPD group ranged from 24 to 32 weeks and the non-surfactant BPD group were 27-29 weeks, birth weights were not mentioned. (155) Husain et al. reported that there were fewer, larger more simplified alveoli, negligible airway epithelial hyperplasia, variable airway smooth muscle hyperplasia, variable interstitial fibrosis and fewer in number dysmorphic capillaries in the BPD group who did not receive surfactant (Table 2). (155) Husain et al. also concluded that the use of post-natal surfactant did not alter the inhibition of acinar development that occurred in infants with BPD. (155)
Table 2: Evolution of pathology in BPD ([4,77,97,99])

<table>
<thead>
<tr>
<th>Classical BPD</th>
<th>New BPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Late saccular phase of lung development</td>
<td>• Canalicular phase of lung development</td>
</tr>
<tr>
<td>• High ventilation and oxygen requirements</td>
<td>• Modest ventilation and oxygen requirements</td>
</tr>
<tr>
<td>• Alternating areas of atelectasis with hyperinflation</td>
<td>• Decreased, large and simplified alveoli</td>
</tr>
<tr>
<td>• Epithelial hyperplasia</td>
<td>(alveolar hyperplasia and decreased acinar complexity)</td>
</tr>
<tr>
<td>• Decreased internal gas exchange area and alveoli</td>
<td>• Less regional heterogeneity of lung disease</td>
</tr>
<tr>
<td>• Airway smooth muscle hyperplasia</td>
<td>• Negligible airway epithelial hyperplasia</td>
</tr>
<tr>
<td>• Extensive fibrotic changes</td>
<td>• Variable airway smooth muscle hyperplasia</td>
</tr>
<tr>
<td>• Interstitial and alveolar oedema</td>
<td>• Variable interstitial fibrosis</td>
</tr>
<tr>
<td>• Hypertensive remodelling of pulmonary arteries</td>
<td>• Decreased numbers of capillaries (dysmorphic)</td>
</tr>
<tr>
<td>• Northway et al. birth weights (average) 1900 g (128)</td>
<td>• Less septal fibrosis that appears more diffuse</td>
</tr>
<tr>
<td>• Northway et al. gestational age (average) 32 weeks’ of gestation (128)</td>
<td>• Jobe et al. birth weights (average) 600 g (131)</td>
</tr>
<tr>
<td>• Northway et al. infants at risk – more mature (128)</td>
<td>• Jobe et al. gestational age (average) 24-26 weeks’ of gestation (131)</td>
</tr>
<tr>
<td>• Northway et al. causes – Oxygen toxicity, mechanical ventilation</td>
<td>• Jobe et al. infants at risk extremely low gestational age &amp; ELBW</td>
</tr>
<tr>
<td>• Jobe et al. causes – Interference with development</td>
<td>• Jobe et al. causes – Interference with development</td>
</tr>
</tbody>
</table>

The terms classical and newer BPD not only reflect advances in perinatal medicine over the last four decades, but also emphasise the different stages in lung development in which preterm birth and subsequent extra uterine lung development occur. (5) Infection, inflammation and cytokine exposure in utero plus post-natal lung injury caused by individual factors such as oxygen, resuscitation, mechanical ventilation and infection all lead to an inflammatory response that may be associated with abnormal injury healing. Normal extra-uterine alveolarisation and vascular development can be compromised, with long-term consequences for the infant. (4)

Exogenous surfactant administered to babies with moderate to severe RDS has been shown to reduce the severity of the disease, the ventilation requirements and the risk of air leaks. Exogenous surfactant can be administered for both prevention and cure. For babies born at less than 31 weeks’ gestation most benefit is gained by early administration of exogenous surfactant (within two hours of birth). For babies born at 31 or more weeks’ gestation exogenous surfactant is usually only administered to those with a confirmed diagnosis of RDS. The ANZNN, in 2009 reported that 33.5% of their database registrants had exogenous surfactant administered, and in this same year 2738 babies who received IPPV for RDS. Exogenous surfactant was given to 2520/2738 of these babies (92.0%). It is important to remember as previously stated ANZNN.
registrants are selected high risk neonates and based on the selection criteria will be more likely to have received perinatal intervention, including surfactant therapy.

5.1.4.8 Other complications of prematurity

5.1.4.8.1 Patent ductus arteriosus (PDA)

The ductus arteriosus (DA) is a vascular structure that connects the aorta to the top of the pulmonary artery, near the start of the left branch pulmonary artery, see Figure 19. Before birth the DA forms a vascular shunt that lets the right ventricular output bypass the developing fetus’ fluid-filled lungs, an area of high resistance, to the systemic circulation. In full term infants, after the infant breathes air the DA is no longer required, and the ductal shunt usually closes spontaneously within the first few minutes or hours of life. Closure of the DA is triggered by the increase in oxygen tension postnatally as the infant breathes, causing contraction of the ductal smooth muscle. Following closure of the DA the right ventricular output flows to the pulmonary circulation and is not diverted to the aorta. The DA becomes a PDA if it persists for more than a few days. The aetiology for a PDA beyond the first few days of neonatal life is not fully understood. A PDA is present in many preterm infants born less than 28 weeks completed gestation. Acute perinatal stress, moderate-severe RDS with a need for mechanical ventilation within a few hours of birth, neonatal sepsis, and higher total fluid administration during the first few days postnatally may be some of the factors associated with a persistent PDA. Persistent patenty of the ductus arteriosus is a major cause of morbidity and mortality in preterm and very low birth weight infants. A persistent PDA increases blood pressure within the venous and arterial pulmonary capillary beds. The impact of a PDA depends on the magnitude of the shunt and the resistance of the PDA or pressure gradient between the aorta and pulmonary artery. Left-to-right shunting of blood through the PDA results in extra fluid in the pulmonary circulation and left ventricle pressure increases. The pressure gradient is also influenced by systolic and diastolic pressures, and cardiac output. If the increased pulmonary blood flow, as a result of the PDA leads to increased pulmonary fluid and/or pulmonary oedema or haemorrhage, there may be a decrease in lung compliance, which will increase the infant’s work of breathing. The incidence of PDA is difficult to ascertain due to differences in methodologies relating to populations studied, age at which they are studied, and how a PDA is detected, although it is estimated to range from 50% to 80% of infants born less than 32 weeks’ gestation. Although numerous epidemiologic studies show associations between persistent PDA and BPD, the evidence for PDA having a causal role is still lacking. Interventions for PDA in preterm infants include fluid restriction and cyclooxygenase (COX) inhibitors, for example indomethacin and ibuprofen. In selected cases, surgical ligation of the ductus is also an option, although the Victorian Infant Collaborative Study Group reported that
following surgery with general anaesthesia increases the risk of neurologic and developmental
disability in extremely low birth weight (ELBW) and extremely preterm infants. PDA is associated with worse respiratory outcomes. Recent randomized controlled trials have attempted to address the timing of interventions rather than the role of exposure to PDA in the development of BPD. Marshall et al. reported that infants with very low birth weights (<1501 g) who were ventilated at 48 hours and had a PDA had an increased risk of BPD (Odds Ratio 1.9; 95% CI 1.2, 3.1). Bancalari et al. showed the incidence of PDA and infection elevated the risk of ELBW infants developing BPD. Rojas et al. demonstrated that lower birth weight and PDA increased the risk for developing BPD in ventilated ELBW preterm infants, with an odds ratio of 6.2 (95% CI, 2.1 to 18.4). Evans et al. reported that larger PDAs in infants born 24 to 33 weeks’ gestation whose birth weights ranged from 993 g to 1490 g were significantly associated with Intraventricular haemorrhage (IVH) (p=0.023). Shortland et al. reported data from 120 infants born with mean birth weight 1220 g and median gestation of 29 weeks and showed that infants with a PDA were significantly more likely to develop cystic periventricular leukomalacia (PVL) than those without a PDA (p<0.02). Dolberg et al. reported that the occurrence of necrotizing enterocolitis (NEC) was independently associated with the presence of a PDA among infants of 24-34 weeks’ gestation born between 1995 and 2000, not only in those not treated with indomethacin (odds ratio, 1.85) but also in those who were treated with indomethacin (odds ratio, 1.53).

Figure 19: Patent ductus arteriosus, adapted from (168)

5.1.4.8.2 Intraventricular haemorrhage (IVH)
Intraventricular haemorrhage (IVH) is a major complication of prematurity, and occurs in approximately 45% of EP/ELBW neonates. IVH of the newborn is bleeding into the fluid-filled
areas (cerebral ventricles) in the brain. IVH commonly occurs within the first several days of life and is rarely present at birth or after 1 month of age, even if the baby was born preterm. Large bleeds in the centre of the brain can cause morbidity or mortality in preterm babies. IVH is more common in preterm babies who have had RDS, abnormal blood pressure, and other conditions that cause disturbances in cerebral blood flow. (169) The cause of IVH is multifactorial and is primarily accredited to the fragile nature of the germinal matrix vasculature and the disturbance in the cerebral blood flow. (169) Intra-vascular factors that may cause IVH include: impairment of cerebral auto regulation, fluctuation of cerebral blood flow (related to fluctuating arterial blood pressure), increased cerebral blood flow which may be due to hypercarbia or excess volume expansion, increased cerebral venous pressure which may be due to pneumothorax, asphyxial heart failure and coagulation abnormalities. (169) Vascular factors that may cause IVH include damage to the germinal matrix, a highly vascular structure with poor capillary support within the brain, and within which the capillaries are vulnerable to hypoxic-ischaemic injury. (169) When the haemorrhage in the germinal matrix is large, the epithelium-like lining of the ventricular system of the brain (ependymal) breaks, and the cerebral ventricle fills up with blood. (169) Thus, IVH is typically a progression of germinal matrix haemorrhage. (169) The majority of infants with IVH are asymptomatic and the diagnosis is based on screening cranial ultrasound. (169) The incidence of IVH in VLBW infants remains stable at around 20%. (169) The ANZNN report that initial head ultrasound is generally performed during the first week of life to detect signs of IVH that is graded by severity. (98) There are four grades of IVH, based on the degree of bleeding. Grades 1 and 2 involve a smaller amount of bleeding. Most of the time, there are no long-term problems because of the bleeding. Grades 3 and 4 involve more severe bleeding. The blood presses on or leaks into brain tissue. Blood clots can form and block the flow of cerebrospinal fluid. This can lead to increased fluid in the brain (hydrocephalus). (169) In 2008, the ANZNN reported 3,666 infants (<32 weeks’ gestation) were eligible for such an ultrasound, approximately 20% were abnormal, and around 4% were graded as severe (IVH grade 3 or 4), and most (~64%) of the severe group were EP (gestational ages 24-26 weeks at birth). (98) IVH reduces the survival of preterm infants and increases the risk of neurological sequelae. (169) Higher mortality rates have been reported in preterm infants developing IVH compared to those preterm infants who do not. (169, 170) Preterm infants with moderate to severe IVH (grades 3–4) may be at higher risk of developing post-haemorrhagic hydrocephalus, cerebral palsy and mental disability, whereas preterm infants with mild IVH (grades 1–2) may be at a higher risk of developmental disabilities. (169, 171, 172) Approximately 45–85% of premature infants with moderate-to-severe IVH develop major cognitive impairment and approximately three quarters of these infants need special education in school. (169, 173)
5.1.4.8.3 Cystic periventricular leukomalacia (PVL)

Cystic periventricular leukomalacia (PVL) is recognised as a leading cause of cerebral palsy in infants where small areas of brain tissue die (necrosis) around the ventricles and create "holes" or "cysts in the brain". A major cause is thought to be changes in blood flow to the area around the ventricles of the brain. PVL is relatively uncommon in preterm infants, occurring in approximately 4% of EP infants. Those especially at risk are EP or ELBW, especially those who have had pre or postnatal infection and required PDA surgery.

Cystic periventricular leukomalacia (PVL) was diagnosed before discharge and defined as any cystic lesions developing in periventricular white matter of the brain after birth.

5.1.4.8.4 Necrotising enterocolitis (NEC)

Necrotising enterocolitis (NEC) is a condition of the neonatal period characterised by bowel necrosis followed by multisystem organ failure. Necrotising enterocolitis (NEC) is a common gastrointestinal emergency seen in the neonatal intensive care unit. Despite advances in neonatal care, NEC is still a leading cause of morbidity and mortality among EP and ELBW infants. NEC affects approximately 10% of all EP or ELBW infants. The risk for NEC is inversely proportional to gestational age and birth weight. Epidemiologic studies have demonstrated different factors that increase an infant’s risk for the development of NEC, preterm birth, infection, PDA, and enteral feeding may play central roles in disease pathogenesis.

5.1.4.8.5 Pulmonary arterial hypertension (PAH)

Infants with BPD can develop pulmonary arterial hypertension (PAH) because of disruption of the pulmonary circulation structure and an increase in the pulmonary vascular resistance because of alveolar injury and unintentional periods of hypoxia. An important factor in the development of PAH is the timing of BPD development, for example early versus late evolving BPD. Evans et al. showed, over the first 5 days of life, higher estimated pulmonary artery pressure in preterm infants with RDS when compared with those without RDS. Evans et al. also demonstrated a fall in pulmonary artery pressure as these infants recovered from RDS. Gill et al. using echocardiography showed infants with BPD who were assessed over the first four weeks of life had a smaller drop in pulmonary artery pressure than infants who did not have BPD. Subhedar et al. showed, using serial examinations with non-invasive assessments of pulmonary artery pressure, that pulmonary artery pressure falls in infants with and without BPD, but remains persistently increased in those with BPD until the end of the first year of life. They also suggested that pulmonary artery pressure is higher in more immature infants in the first year of life, independently of the presence of BPD.
5.1.4.8.6 Neurosensory impairments

The improved survival rate of preterm infants has meant an interest in long-term outcomes with regard to neurosensory and cognitive sequelae. During school-age, adolescence and beyond, subjective physical and psychosocial health aspects are important, in addition to the objective measures of health, such as lung function.

EP or ELBW infants born in the post-surfactant era survive mostly without major disabilities, although follow-up studies have shown, at preschool age, many children with disabilities caused by impairments such as cerebral palsy, mental impairment, blindness and deafness exist. School-age follow-up studies in EP/ELBW populations have revealed socio-emotional, cognitive and learning problems as well. The first studies of young adults who were born in the pre-surfactant era (<1990) are starting to enter the literature (and report risks for physical and neurodevelopmental problems, increased levels of chronic illness, lower IQ and academic achievement compared with term born controls). The weakness of the data reporting outcomes in preterm adults is that it is restricted to small numbers of infants followed up from individual hospitals. There is a wide range of differing functional outcomes that have been reported among consecutive cohorts of preterm LBW infants. Previous studies have already shown that preterm and LBW infants are at risk for neurodevelopmental problems in early adulthood. Hack et al. showed despite higher rates of chronic conditions, ELBW children rate their health as similar to NBW controls.

Emotional, social and physical development changes during adolescence, with potentially important effects on health, especially of EP/ELBW survivors. Hack et al. found ELBW children reported significantly more risk avoidance that is less risk taking than controls. Hack et al. found no difference in between groups in the domains of satisfaction, comfort, resilience or disorders, although when they examined sub domains they revealed significantly less physical activity levels and more long-term surgical and psychosocial disorders compared with controls. Hack et al. suggest the reasons for less risk taking are not fully understood but may include emotional problems. They suggest relative social isolation of children with disabilities and increased parental supervision may be associated with fewer opportunities for risk taking. Hack et al. found, however reduced risk taking among ELBW subjects was still evident after excluding children with neurosensory impairment. The decreased physical activity reported by Hack et al. in ELBW adolescents may be related to poorer motor performance and reduced exercise capacity. Hack et al. reported that socio-demographic status, female gender and neurosensory impairment were correlated with decreased physical activity. The relationship of socio-demographic status, physical activity and health may relate to community resources, access to healthcare, and differences in family lifestyle.
5.1.5 Fetal origins of adult lung disease hypothesis

As discussed, lung development within the fetal period starts early, around 7 weeks’ gestation and continues until a few years after birth. Lung development may be influenced by many physical, metabolic and inflammatory factors throughout this growth period. Lung tissue growth does not occur at a constant rate over this time. The branching airways are formed at early gestational ages and are largely complete by 27 weeks. Alveolarisation occurs during the final weeks and months of gestation and continues postnatally for 2 to 3 years. Therefore, it is plausible that an insult or stimulus during fetal life or the early postnatal years could alter the structure and physiology of the respiratory system and this may have long-term effects.

The “Fetal origins hypothesis”, also known as the “Barker hypothesis”, suggests that adaptations made by the fetus in response to lower than normal nutrition occurring for a variety of reasons, including poor maternal diet and/or problems with the mobilisation and transfer of nutrients from mother to fetus, lead to permanent changes in metabolism and in organ structure, which in turn lead to disease later in life, such as cardiovascular disease and diabetes mellitus. It is suggested that such “programmed” changes in utero resulting in intrauterine growth restriction may constrain airway growth and peripheral lung development, predisposing infants to chronic airflow problems in adult life.(182,183) With this threat to survival, the fetus is supposed to make adaptations to limit its growth, prioritise the development of essential tissues and organs, and hasten maturation.(182,183)

The hypothesis is supported by epidemiological evidence showing an association between newborn size, and infant growth and nutrition, and adult health outcomes, and by experiments in animals showing that maternal under- and over-nutrition and other interventions, for example exposure to glucocorticosteroids, during pregnancy lead to abnormal metabolism and body composition in the adult offspring.(182)

In keeping with the fetal origins of adult disease hypothesis there have been reports of birth weight being a determinant of lung function. Similarly there is concern amongst researchers that the abnormal lung function seen in survivors with ELBW or EP birth who develop BPD may result in chronic lung diseases of adulthood.(25,184-190)

Normal lung growth increases from birth until approximately 20 years of age when the peak in lung function occurs, which is then followed by a natural decline as individuals age (Figure 5). Insults such as ELBW, EP birth and infection may lead to interrupted lung growth and development. Other early insults such as mechanical ventilation-induced atelectrauma, barotrauma and volutrauma may lead to further damage and interfere with lung growth and development.
Abnormal lung growth and development in turn could result in a reduced peak lung function as an individual reaches early adulthood. If further damage to the lungs occurs from an external insult, such as cigarette smoking, the natural decline in lung function may be accelerated. This may lead to accelerated decline and earlier presentation to adult physicians with symptoms that may mimic smoking-related disease, such as Chronic obstructive pulmonary disease (COPD). Those who had the most protracted lung disease as infants (i.e. BPD) should be advised to avoid cigarette smoke.

COPD and emphysema are common diseases in adult respiratory medical practice. COPD and emphysema are disease processes related to smoking, severe asthma or chronic infection, and result in destruction of alveolar walls. BPD is the result of disruption in development of alveolar walls, and may mimic the symptoms of COPD as the populations of mechanically ventilated neonates’ progress through adulthood. The cohort first described by Northway et al. are now in their 40s respiratory physicians in adult medicine must increasingly be aware of perinatal history and investigate a differential diagnosis for those young adults presenting with emphysema. Neonates who receive mechanical ventilation and oxygen therapy should be followed into adulthood to further classify outcomes and provide information for differential diagnoses.

Narayanan et al. suggested that alveolarisation continues beyond early childhood and reported data from a review of animal research that suggests alveolarisation continues throughout the normal period of lung growth and development in mammals, as shown in Figure 1. This group recently reported that catch-up growth, in terms of alveolar size and number, returns to normal by adolescence after preterm birth and the development of BPD. They reported lung function and data from helium-3 magnetic resonance imaging that represents average alveolar dimensions from 4 groups of children aged 10-14 years of age; group 1 were the term-born controls, group 2 were “mild preterm” (GA 32-36 weeks’), group 3 were extremely preterm (GA <32 weeks’) and group 4 were extremely preterm and had BPD (GA <32 weeks; oxygen dependency at 4 weeks). They showed alveolar size in adolescence was similar in the extremely preterm groups compared with term-born controls and postulated that extremely preterm birth was associated with deranged alveolar structure early in life and that their finding must represent catch-up growth. This may be the case or it may mean that alveolar dimensions measured by helium-3 magnetic resonance imaging is not detailed enough to provide an accurate estimate.

Despite the concerns about the long term effects of EP/ELBW birth it is clear that the short-term respiratory outcomes of neonates have improved over time and more particularly with
the advent of altered ventilation strategies such as permissive hypercapnoea, antenatal corticosteroids and postnatal surfactant treatment. The magnitude of the impairment found in survivors after ELBW and/or VPT birth can be significant but most are able to live normal lives. With improvements to existing treatment and new treatments implemented in the future we may expect further improvements in long-term respiratory health and neurological function in the years to come.

5.1.6 Respiratory function and exercise capacity in preterm survivors

The lungs of EP/ELBW infants are functionally and structurally immature. After preterm birth, normal lung growth and development are interrupted and the immature lung is exposed to adverse stimuli at the time when they are most susceptible to injury, for example from oxidants, barotrauma and/or infection-inflammation. The outcome of infants born EP or ELBW tends to depend on the extent of prematurity, with infants born at earlier gestations more likely to experience complications after birth.(75) In addition to a higher rate of mortality, EP or ELBW infants have an increased risk of visual impairment, pulmonary hypertension, intraventricular haemorrhage, periventricular leukomalacia, or gastrointestinal problems, which are predictive of later neurological impairment and cerebral palsy in survivors. However, for EP and ELBW infants the most common complication is respiratory impairment. This thesis will focus on respiratory function and exercise capacity impairment in EP and ELBW survivors.

It is conceivable that the pattern of lung growth during childhood and adulthood could vary as follows:

- An early insult on lung growth in the prenatal or early postnatal period followed by normal growth in childhood and a normal rate of decline in adulthood;
- An early insult on lung growth in the prenatal or early postnatal period followed by normal lung growth in childhood with an accelerated decline in adulthood;
- Failure to achieve maximum growth during childhood followed by the normal rate of decline seen in adulthood;
- Failure to attain maximum growth followed by early onset or accelerated decline.

Follow-up studies on lung function and exercise show conflicting results. The reported effects of EP or ELBW, whether survivors who developed BPD or not, on respiratory function and exercise capacity outcomes differ greatly between studies published to date.(123) Inconsistencies arise from inclusion and exclusion criteria, which differ noticeably between studies. There are differences in gestational age and birth weight distributions of the study groups that are likely to affect both adverse respiratory outcome and the association with EP or ELBW and BPD, as the incidence of these is inversely related to gestational age and birth weight. Some studies further
selected their cohorts by including only hospital births or selected patient groups, such as those with severe BPD. When considering outcomes, such as hospitalisation, infection, wheezing and the results of lung function tests it is important to remember that BPD is a broad term, the definition and epidemiology of which have changed significantly over the past four decades. For instance, the use of exogenous surfactant and antenatal corticosteroids alongside improvements in mechanical ventilation and oxygen delivery in the early 1990s have led to dramatically improved survival rates and reduced lung injury amongst those infants who are born very preterm, at extremely low birth weights. Moreover, the complexity of the change in BPD definition is compounded by the observation that lung function testing not only examines the effects of ELBW, extreme prematurity and BPD on the lung, but also looks at the effects of the post-hospital environment, which may include repeated respiratory infection and cigarette smoke exposure, on lung function.(194,195).

Respiratory morbidity is common in infants who have been treated with mechanical ventilation and oxygen therapy for respiratory failure, especially in those who develop BPD.(22,196,197) The infant moves from RDS to BPD as the effects of inflammation, mechanical ventilation induced volutrauma, and oxygen (chemotrauma) lead to chronic lung injury and repair. This pattern of injury and repair will eventually overshadow the effects of prematurity and growth restriction alone.(137,198-200)

During the first few years following discharge from hospital children with BPD may have a prolonged requirement for supplemental oxygen and are more likely to be treated for pneumonia and be readmitted to hospital for respiratory infections such as respiratory syncytial virus (RSV)-induced bronchiolitis.(194,201-207) These young infants are reported to have higher incidences of wheezing, ‘asthma-like’ symptoms, hyper-reactivity of their airways and increased levels of inflammatory markers.(95,202,207,208) By the time these infants have reached school age their risk of hospital admission is comparable to those children without a history of mechanical ventilation or BPD. There are conflicting reports as to whether there is an increased(209-211) or the same incidence(128,212) of asthma in ELBW/preterm survivors. Other studies suggest that reduced airway function in the first year of life may lead to transient wheeze, but no long-term risk of atopy.(213)

Lung function measurements in infants are currently restricted to specialist laboratories. Those researchers who have performed measurement of pulmonary function in infants with BPD have shown reductions in lung volumes, impaired ventilation distribution, reduced dynamic compliance, increased airways resistance, evidence of air trapping and reduced expiratory flows compared with contemporaneous individuals and control subjects.(187,214-220) These values, although abnormal on many occasions, do not always fall within clinically significant ranges. This
BPD is a major cause of long-term respiratory morbidity in children, adolescents and adults who were ventilated and/or required long-term oxygen therapy as neonates with respiratory failure. There are many cross-sectional studies investigating respiratory outcome in these individuals who have shown increased prevalence of airflow obstruction, air-trapping (hyperinflation and/or loss of lung elasticity) and impairments in the gas exchange properties of the lung as shown in Table 3. Other researchers show no significant differences between those who had BPD and those who did not (Table 3). The ELBW/EP birth survivors with BPD have demonstrated changes in lung structure and function that may result in ventilation disruption, inefficiency or inhomogeneity. The disruption of alveolar development (larger but fewer alveoli), decreased surface area for gas exchange and disrupted angiogenesis can be assessed by measuring the diffusing capacity of the lung for carbon monoxide (DLco). Several investigators have measured DLco in low birth weight or preterm survivors, most have found significant reductions compared with NBW contemporaries, but none have demonstrated mean reductions outside the limits of normal for this test. Ventilation efficiency can be assessed non-invasively by the multiple breath nitrogen washout (MBNW) test. This allows investigation of the so-called “silent-zone” in the lung that cannot be readily measured with conventional respiratory function tests. Indices derived from MBNW give information about the efficiency of ventilation overall and in the conductive and diffusive zones of the lung. MBNW indices have been shown to be abnormal in asthma, and to be more sensitive than spirometry for detecting early changes to the peripheral airways associated with smoking. There are currently only a few studies using this technique in preterm or low birth weight survivors. Shao and colleagues assessed the usefulness of MBNW in 15 preterm infants at 35.1±2.4 (mean±SD) weeks of post-menstrual age for determining severity and monitoring purposes. They concluded that it was a simple and sensitive measure of impaired gas mixing in BPD survivors. Hulskamp found a reduction in functional residual capacity (FRC) that was independently associated with prematurity, ELBW and severity of BPD. Lum and colleagues suggest that the reduction they found in gas mixing efficiency may reflect small airway changes, secondary to neonatal positive pressure ventilation.

Studies detailing long-term pulmonary outcomes of extremely preterm infants born in the post surfactant era have only begun to emerge as these children approach adolescence and can perform complex pulmonary function tests. Studies initiated in the pre-surfactant era or in children born in the early 1990s demonstrated a mild to moderate reduction in FEV1, limited...
reversibility after bronchodilator treatment, elevated residual volume/total lung capacity (RV/TLC) ratio, and decreased diffusion.(229) Although bronchial hyper-reactivity is common in survivors of BPD, the fraction of exhaled nitric oxide (FeNO), a sign of eosinophilic inflammation when high, is not increased.(5,75,78,135-137,229) Cardiopulmonary exercise testing (CPX) data are inconsistent, with some studies demonstrating no change in peak oxygen consumption (V'O₂) or breathing reserve, whereas others demonstrated a lower peak V'O₂ in extremely preterm infants compared to term controls.(229)

Comparisons between studies of preterm or LBW survivors are difficult because of the disparate populations and differing treatments, e.g. ventilation modes or surfactant therapy. There are also other factors, alongside prematurity and its associated treatment, that may influence symptoms and other functional outcomes, such as socioeconomic status and tobacco smoke exposure. It is difficult to work out the influence each of these factors exerts on the likelihood of preterm birth or reductions in birth weight, and how they affect respiratory health outcomes. An example of this is maternal smoking, which is associated with LBW and preterm birth, but can also be associated with respiratory symptoms in NBW term-born babies, making it difficult to define the absolute contribution of maternal smoking and preterm birth per se. It is for this reason the choice of the “normal” control group is important, especially for longitudinal studies. Ideally the “normal” control group should be matched for as many variables (e.g. ethnicity) as possible in the hope they are not too dissimilar to the index group, and they should be retained for the entirety of the study. Practically speaking it is difficult to retain the patient groups over time, let alone the controls. The term “asthma” is often used in follow-up studies, but not frequently defined adequately. Wheeze does not necessarily mean that there is atopic airway inflammation present. This is especially important in EP/ELBW children with BPD has been shown to share some features, such as airflow limitation without increases in atopy, suggesting a difference in the pathophysiology of the two obstructive-type airway diseases.

Few studies have reported findings from the same individuals who were born EP or ELBW as a neonate and developed BPD through to late adolescence or adulthood. Those studies have reported three significant findings: Firstly, airflow obstruction is a consistent feature of respiratory function in survivors of BPD.(188,230) Secondly, airflow obstruction appeared to improve in some cases over time.(188) Thirdly, despite the improvement in lung function over the teenage years some respiratory impairment persists in adults who had previously had BPD as an infant.

A number of neonatal variables have been associated with abnormal respiratory function later in life. Earlier gestational age at birth has been associated with worse airflow as measured by the FEV₁ (r=0.788, p<0.01) and the FEF₂₅-₇₅% (r=0.745, p<0.01).(231) Moreover, the total duration
of ventilation was negatively associated with abnormal airflow as measured by the FEV₁ (r=-0.763, p<0.01), FVC, FEF₅₀% and FEF₂₅-₇₅%.(231,232) Given that reduced FEV₁ is a marker of all-cause mortality there is concern that survivors or EP/ELBW birth are at risk of chronic airflow obstruction in early adulthood.(219)

5.1.6.1.1 Respiratory symptoms

During the first few years following discharge from hospital children who had BPD may have a prolonged requirement for supplemental oxygen, are more likely to be treated for pneumonia and be readmitted to hospital for respiratory infections such as respiratory syncytial virus (RSV)-induced bronchiolitis.(202,203,233) Respiratory symptoms in infancy following preterm birth and BPD are summarised in Table 3.

Preterm infants, especially those who wheezed at follow-up, have evidence of airway obstruction (a raised airways resistance and gas tapping) in the first 2 years of life.(234) Martinez et al. suggest that reduced airway function in the first year of life may lead to transient wheeze but no long-term risk of atopy.(213) Infants with BPD have higher hospitalisation rates (approximately 50%) within the first years of life.(204) Greenough et al. reported the United Kingdom oscillation study showed that 27% of infants born before 29 weeks’ gestation were coughing and 20% were wheezing at 6 and 12 months.(87) It is unclear whether the severity of BPD or prematurity per se is associated with persistence or severity of respiratory symptoms.(134)

Respiratory symptoms persist and remain common at pre-school age (Table 3). Greenough et al. reported that 25% (47/190) of subjects with BPD who had a median gestational age 27 weeks (range 22-31 weeks) coughed more than once a week and 6% (10/190) wheezed once a week from 2-4 years of age.(235) Hospitalisation rates declined after the 2 years of age.(236)

By the time EP/ELBW infants reach school age their risk of hospital admission is comparable to those children without a history of preterm birth, mechanical ventilation or BPD.(203,237) There are conflicting reports as to whether there is an increased (209-211) or the same incidence (212,238) of asthma in EP/ELBW survivors (Table 3). Guimarães et al. reported no differences in preterm school-age children wheezing (~62% with BPD vs. ~72% without BPD; p=0.06), dyspnoea (~70% with BPD vs. ~86% without BPD; p=0.09) or hospital admissions for respiratory reasons (~31% with BPD vs. ~19% without BPD; p=0.5). These researchers also assessed atopy by the allergy skin-prick test and found no significant differences in preterm school-age children with BPD compared with those without (allergy; positive skin-prick test ~31% with BPD vs. ~27% without BPD; p=0.7).
It is important to emphasise that publications relating to adolescent and adult survivors of preterm birth with or without BPD all received intensive neonatal care in the pre surfactant era. As such infants are described as having classical BPD rather than the newer BPD.

Adolescents who had BPD show increased respiratory symptoms, persistent airflow limitation, airway hyper-reactivity, with an increased response to histamine and increased incidence of previous pneumonia (Table 3). (238-240)
Table 3: Selected cross-sectional respiratory symptoms data from studies of ELBW/preterm survivors, including some with BPD.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Cohort years of birth</th>
<th>Age (years)*</th>
<th>Participants</th>
<th>GA (weeks)</th>
<th>BW (grams)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fakhoury et al.</td>
<td>(1999-2003)</td>
<td>8-34 months</td>
<td>PREM BPD 44</td>
<td>25.6wk±1.7wk</td>
<td>767g±200g</td>
<td>Significant bronchodilator response in 30% at 6 months, 21% at 12 months and 20% at 12 months.</td>
</tr>
<tr>
<td>Gross et al.</td>
<td>(1985 to 1986)</td>
<td>6 &amp; 15 months</td>
<td>PREM BPD 43</td>
<td>28.2±2.1wk</td>
<td>1173±345 g</td>
<td>↑ rehospitalisation 53% PREM BPD vs. 26% PREM No BPD in 1st &amp; 2nd years; PREM BPD &amp; PREM No BPD more likely to cough &amp; wheeze at 7 years</td>
</tr>
<tr>
<td>Furman et al.</td>
<td>(1988 to 1990)</td>
<td>2</td>
<td>PREM BPD 98</td>
<td>26.9±2.0wk</td>
<td>891±222g</td>
<td>PREM BPD 50% hospitalised in the 1st year; 37% hospitalised in 2nd year; pneumonia most common cause; ↑ airway hyper-reactivity</td>
</tr>
<tr>
<td>Kitchen et al.</td>
<td>(1977 to 1982)</td>
<td>2, 5 &amp; 8</td>
<td>Group 1: 86 PREM (51.4% BPD)</td>
<td>500-999g</td>
<td>1000-1500g</td>
<td>More hospitalisations in groups 1 &amp; 2 vs. controls; more frequent wheezing in groups 1 &amp; 2 vs. controls; No significant differences at 5 &amp; 8 years</td>
</tr>
<tr>
<td>Furman et al.</td>
<td>(1988 to 1990)</td>
<td>2</td>
<td>PREM BPD 98</td>
<td>26.9±2.0wk</td>
<td>891±222g</td>
<td>PREM BPD 50% hospitalised in the 1st year; 37% hospitalised in 2nd year; pneumonia most common cause; ↑ airway hyper-reactivity</td>
</tr>
<tr>
<td>Ng et al.</td>
<td>(1987 to 1995)</td>
<td>5.4±2.3</td>
<td>PREM BPD 55 (50.9% Surfactant)</td>
<td></td>
<td></td>
<td>44% current asthma; 55% past asthma by questionnaire, examination or positive airway challenge test</td>
</tr>
<tr>
<td>Chan et al.</td>
<td>(1979-1980)</td>
<td>7 (0.2)</td>
<td>VLBW 134</td>
<td>31.8±2.8wk</td>
<td>1472±348g</td>
<td>VLBW ↑ whooping cough, ↑ chest infections, ↑ hospitalisations for chest illness; VLBW ↑ cough with exercise unrelated to colds; VLBW ↑ cough with or without colds</td>
</tr>
<tr>
<td>Palta et al.</td>
<td>(1988-1989)</td>
<td>9.2 (8-10)</td>
<td>PREM 384 (31-33% BPD)</td>
<td>1111g (251g)</td>
<td>1115g (260g)</td>
<td>PREM ↑ respiratory symptoms from questionnaire; significant trend in decreasing symptoms across 3 time periods.</td>
</tr>
<tr>
<td>Northway et al.</td>
<td>(1964-1973)</td>
<td>18.3 (2.7)</td>
<td>PREM BPD 26</td>
<td>33±34wk</td>
<td></td>
<td>2/26 PREM BPD had current respiratory symptoms, e.g. wheeze, pneumonia and exercise limitation</td>
</tr>
<tr>
<td>Vrijlandt et al.</td>
<td>(1983)</td>
<td>19±0.3</td>
<td>PREM No BPD 32</td>
<td>30±2</td>
<td>123±232g</td>
<td>PREM ↑ exercise related shortness of breath, wheezing, “doctor diagnosis” of asthma, further ↑ PREM BPD females, by questionnaire</td>
</tr>
<tr>
<td>Doyle et al.</td>
<td>(1977-1982)</td>
<td>14</td>
<td>Group 1: 86 PREM (51.4% BPD)</td>
<td>500-999g</td>
<td>1000-1500g</td>
<td>No difference in asthma prevalence PREM BPD vs. PREM No BPD; respiratory symptoms assessed by presence of cough, wheeze, asthma medications &amp; hospitalisations</td>
</tr>
<tr>
<td>Halvorsen et al.</td>
<td>(1982 to 1985)</td>
<td>17.7 ± 1.2</td>
<td>PREM Mild BPD 24</td>
<td></td>
<td></td>
<td>PREM ↑ previous pneumonia, hospitalisation, “doctor diagnosis” of asthma</td>
</tr>
<tr>
<td>Northway et al.</td>
<td>(1964-1973)</td>
<td>18.3 (2.7)</td>
<td>PREM BPD 26</td>
<td>33±34wk</td>
<td></td>
<td>2/26 PREM BPD had current respiratory symptoms, e.g. wheeze, pneumonia and exercise limitation</td>
</tr>
<tr>
<td>Kitchen et al.</td>
<td>(1977 to 1982)</td>
<td>2, 5 &amp; 8</td>
<td>Group 1: 86 PREM (51.4% BPD)</td>
<td>500-999g</td>
<td>1000-1500g</td>
<td>More hospitalisations in groups 1 &amp; 2 vs. controls; more frequent wheezing in groups 1 &amp; 2 vs. controls; No significant differences at 5 &amp; 8 years</td>
</tr>
<tr>
<td>Northway et al.</td>
<td>(1964-1973)</td>
<td>18.3 (2.7)</td>
<td>PREM BPD 26</td>
<td>33±34wk</td>
<td></td>
<td>2/26 PREM BPD had current respiratory symptoms, e.g. wheeze, pneumonia and exercise limitation</td>
</tr>
<tr>
<td>Vrijlandt et al.</td>
<td>(1983)</td>
<td>19±0.3</td>
<td>PREM No BPD 32</td>
<td>30±2</td>
<td>123±232g</td>
<td>PREM ↑ exercise related shortness of breath, wheezing, “doctor diagnosis” of asthma, further ↑ PREM BPD females, by questionnaire</td>
</tr>
</tbody>
</table>

* years unless otherwise stated
5.1.6.1.2 Respiratory function tests

Hilgendorff et al. reported data from 27 VP/VLBW infants aged 38 (range, 32-44) weeks’ gestation, 23 of who had BPD of varying degrees, defined as mild (requirement for O₂ supplementation at 28 days postnatally), moderate (requirement for O₂ supplementation < FiO₂ 0.3 at 36 weeks’ postmenstrual age), or severe (O₂ supplementation > FiO₂ 0.3 at 36 weeks’ postmenstrual age); there is no mention of surfactant therefore this cohort may have been born in the pre-surfactant era. They performed body plethysmography in sedated infants to obtain measures of airways resistance and lung volumes and found airways resistance values within normal limits but significantly reduced functional residual capacity compared with normal term control data.

Hofhuis et al. evaluated 39 preterm/VLBW neonates at 2 different ages, the first when the ELBW infants were aged at 6.2±0.9 months, the second when they were 12.6±1.1 months of age (mean GA 26.8±1±SD1.7 weeks at birth; mean birth weight at approximately 6 months 870±SD240 g, mean birth weight at approximately 12 months corrected age 1100±420 g) all of whom had BPD, defined as the need for continuous supplemental oxygen at 28 days and/or requirement at 36 weeks’ gestational and a chest x-ray at 1 month of age typical for BPD. The researcher had 16 neonates who received conventional mechanical ventilation, most (n=15) of whom were treated with Survanta™ surfactant therapy and 15 infants who received high-frequency oscillatory ventilation (HFOV), 9 of whom were treated with surfactant and 61 full-term NBW controls subject recruited from a previous study. Interestingly they reported higher maternal smoking rates during pregnancy in the preterm group compared with the full term controls (28.2% vs. 4.9%; p=0.001), although they do not report how or when this data was obtained, i.e. was this information collected during pregnancy, at birth or at the follow-up. They performed lung function manoeuvres to obtain lung volumes and infant spirometry (Raised volume rapid thoracoabdominal compression technique, RVRTC). Hofhuis et al. found reduced flow rates (VmaxFRC) in infants with BPD that worsens over the first 12 months, this outcome was worse for those preterm/VLBW subjects who received conventional ventilation as compared with those who received high frequency oscillatory ventilation.

Sanchez-Solis et al. studied of 75 EPT/VLBW infants aged 7.0±SD5.9 corrected months with mean gestational age at birth 27.9±SD2.3 weeks and mean birth weight -0.02±SD1.2 z-score compared with “published regression formulas”. They had respiratory function results for 43 infants who had BPD defined as the need for supplemental oxygen at least 28 days after birth with a severity rating based on level of ongoing respiratory support compared with 32 infants without BPD, no mention was made of surfactant therapy. They performed forced expiratory manoeuvres using infant spirometry (RVRTC) and reported reduced forced expiratory flows for
infants with BPD compared with infants without BPD and no significant differences in measures of volume.(248)

Balinotti et al. measured alveolar gas volume and diffusing capacity of the lungs using a 4-second single breath test of carbon monoxide diffusion to evaluate lung parenchymal growth to establish what was normal up to 2 years of age. They showed that gas diffusion increased in proportion to alveolar volume, this suggests that alveolar numbers were increasing.(3,249) Balinotti et al. demonstrated that after adjustment for body length, subjects with BPD had significantly lower gas diffusion capacity even after it was divided by alveolar volume, but no difference in alveolar volume.(3,249)

Fakhoury et al. followed a cohort of EP/ELBW subjects aged 8 to 34 months with a mean gestational age at birth of 25.6±SD1.7 weeks and mean birth weight 767±SD200 g, all of whom received surfactant (no details further surfactant therapy details).(241) They obtained lung function results for expiratory flows using RVRTC at 6, 12 and 24 months post discharge on 44 subjects with BPD, defined as chest x-ray findings consistent with a diagnosis of BPD and an oxygen requirement beyond 28 days of life or 36 weeks’ gestation and showed significant airflow limitation in subjects with moderate to severe BPD compared with mild BPD that did not improve with time.(241)

Latzin et al. reported data from a cross-sectional observation study where they recruited preterm/VLBW infants aged 36-197 postnatal days and included 58 healthy preterm (mean GA 32±SD2.3 weeks at birth; mean birth weight 1660±SD570 g). There were 127 infants with BPD, defined as a requirement for supplemental oxygen at 28 days; no mention was made of surfactant therapy.(250) The BPD infants were stratified further so that 44 subjects were said to have mild BPD, defined as breathing room air by 36 weeks PMA, 53 infants had moderate BPD, defined as requiring supplemental less than 30% oxygen at 36 weeks PMA and 44 with severe BPD, defined as requiring supplemental oxygen greater than 30% at 36 weeks PMA.(250) They performed lung function manoeuvres to obtain values for lung volumes, ventilation efficiency and tidal breathing and found no significant difference between any of the groups for FRC or LCI but significantly higher respiratory rate in the BPD group that increased with increasing severity.(250)

Robin et al. describe data from a cross-sectional study of EP/ELBW infants aged 68±35.6 weeks (absolute post-natal) with a mean gestational age at birth of 26.4±2.1 weeks and mean birth weight 898±353 g compared with a control group of normal healthy infants.(234) They had respiratory function results on 28 infants with a history of BPD, defined as an oxygen requirement at 36 weeks’ postmenstrual age that had 51±31.2 (range, 3-126) mean days of mechanical ventilation and 306±158.8 (range, 48-750) days of oxygen therapy.(234) They performed forced expiratory manoeuvres using the RVRTC technique, also known as infant spirometry.(234) Robin
et al. reported reduced forced expiratory flows for infants with BPD including forced expiratory volume in 0.5 seconds (FEV$_{0.5}$) and FEF$_{25-75}$% compared with normal infants, suggestive of airflow obstruction.(234) This group also measured lung volumes using an infant body plethysmography and showed increased FRC, RV and RV/TLC, which may indicate air trapping or hyperinflation.(234) They also concluded that infants with a history of BPD with symptoms of recurrent wheezing who were being treated with inhaled steroids had the greatest reductions in expiratory flow variables.(234) Whereas infants without wheeze who were not treated with inhaled steroids had mild lung function abnormalities.(234)

Schmalisch et al. identified preterm/VLBW infants who had serial lung function measures at approximately 50, 70 and 100 weeks’ postmenstrual age.(251) They identified 29 subjects with BPD, defined as a requirement for supplemental oxygen at 36 weeks’ postmenstrual age, who had a mean gestational age of 26.4 (SD 2.9) weeks and birth weight mean of 1124 (SD 248) g all of whom had mechanical ventilation alongside 26 subjects without BPD who had a mean gestational age of 29.1 (SD 2.1) weeks and birth weight 816 (243) g, approximately 90% of all subjects had received surfactant (no further details on surfactant therapy were available).(251) They had lung function results for the preterm subjects with and without BPD from 3 separate visits at approximately 50, 70 and 100 weeks’ postmenstrual age and stated there were no significant differences tidal breathing parameters, airways resistance, VmaxFRC and FRC measured by plethysmography (FRC$_{\text{pleth}}$) or gas washout techniques (FRC$_{\text{SF6}}$).(251)

Hülskamp et al. reported results from a longitudinal study where they separated the infants into four groups based on clinical status and gestational age at birth, the first group consisted of full-term controls, and the second group were preterm controls (PTC; mean GA 33.5±1.9 weeks at birth; mean birth weight ~1850±500 g) who had minimal requirements for ventilatory support, a third group of RDS infants who had a history of resolved respiratory distress syndrome but no requirement for supplemental oxygen at 36 weeks’ postmenstrual age (RDS; mean GA 29.6±2.3 weeks at birth, mean birth weight ~1320±450 g), and a fourth group who had requirement for supplemental FiO2 or assisted ventilation at 36 weeks’ postmenstrual age (BPD; mean GA 26.6±2.1 weeks at birth, mean birth weight ~890±290 g).(227) The infants ranged in age at the time of testing from 39 to 47 weeks. Hülskamp et al. used the MBW technique with 4% sulphur hexafluoride (SF$_6$) as a tracer gas using a commercially available prototype ultrasonic flow meter (Ecomedics AG, Duernten, Switzerland) to measure tidal volume (Vt), respiratory rate (RR), FRC and indices of ventilation inhomogeneity (Lung Clearance Index (LCI) and first and second moment ratios (M1/M0, M2/M0), which are different methods of expressing ventilation efficiency).(227) SF$_6$ is an inert gas that does not cross the blood gas barrier and has a high molecular mass, meaning it is easy to isolate from other resident gases within the lungs. They had lung function results for 48 infants (17 PTC, 17 RDS, 14 BPD) were tested on 2 occasions, 15 infants
(6 PTC, 6 RDS, 3 BPD) on 3 occasions and 3 infants (2 PTC, 1 RDS) on 4 occasions. They showed that a reduction in FRC was associated with prematurity, intrauterine growth restriction and severity of neonatal lung disease in this group of infants, and surprisingly they found a large influence of equipment used at the 3 testing sites involved in this study.

Respiratory function testing in preschool children (3-6 years of age) is limited due to the difficulties involved in testing this age group, such as limited attention span and inability to follow precise instructions. The range of tests available is limited so far to resistance interrupter technique (Rint) and forced oscillation technique (FOT). Rint is a non-invasive measure of airway resistance where a transient occlusion (100 milliseconds) is applied during quiet breathing and therefore requires minimal cooperation. FOT is also a non-invasive measure of respiratory resistance (Rrs, elasticity) and reactance (Xrs, compliance) where a pseudo-random noise pressure signal, containing all sound waves of 4 to 48Hz was applied at the mouth by means of a loudspeaker is applied to the respiratory system during quiet breathing. For this reason the few studies following preterm, low birth weight subjects with lung function assessed during the first year do not have follow-up measurements until school age with cooperative patients.

Talmaciu et al. evaluated 40 pre-school children 24 months and older who had BPD, defined as need for mechanical ventilation in the first week of life, clinical signs of respiratory distress, requirement for supplemental oxygen and abnormal chest x-rays by 28 days of life, surfactant therapy was not discussed. They further defined this group by oxygen requirement: the first group (n=21) BPDO2 included subjects who required supplemental oxygen and were “technology dependent” (mean GA 26.9±2.3 weeks at birth; mean birth weight not reported; mean age at test 30.2±6.5 months); the second “non-O2-dependent BPD or control” group had been weaned of mechanical ventilation and supplemental oxygen for at least 6 months prior to pulmonary function testing (mean GA 26.7±2.2 weeks at birth; mean birth weight not reported; mean age at test 30.1±5.5 months). Talmaciu et al. reported approximately 50% of the technology dependent group and 1/19 from the control group as having a tracheostomy at the time of testing, this will affect any tests measuring flow-rates as it is a fixed aperture and will restrict flow at the point of tracheostomy tube. Not surprisingly they found a significant difference in flow rates between the technology-dependent group, i.e. when comparing the group, where approximately half had a tracheostomy, and the control group.

Kairamkonda et al. reported data from a study of 28 EP/ELBW pre-schoolers aged 44 (IQR, 35.5-50.0) corrected months, with a median gestational age at birth of 27 (IQR 26-28) weeks and a median birth weight of 995 (IQR 827-1151) g compared with a group of preterm controls. They had respiratory function results on the 28 subjects all of whom had BPD defined as an oxygen requirement of >30% at 36 weeks’ postmenstrual age and discharged home receiving supplemental oxygen that had 42.5 (IQR 18.5-82) median days of mechanical ventilation and 390
(IQR 340-460) days of oxygen therapy. There was no mention of surfactant therapy. This group also had 18 preterm controls who had slightly but significantly larger gestational ages at birth (29 [IQR 28-31] weeks; p=0.001) and birth weights (1366 [1243-1672] g; p=0.0001) than the BPD group. They performed an assessment of airway obstruction using the interrupter resistance technique (Rint), which Kairamkonda et al. reported satisfactory measurements in 36% of 2 year olds, 65% of 3 year olds and 80% of 4 year olds and showed that subjects with BPD had higher airways resistance (Rint) compared with preterm controls without BPD.

Vrijlandt et al. followed-up 77 subjects at 3-5 years of age and who were born preterm compared with a group of age matched term controls recruited from local nursery and primary schools. The preterm group had 41 participants with BPD (mean GA 28±2 weeks at birth, mean birth weight 1051±536 g), defined as the need for continuous supplemental oxygen at 28 days of age combined with x-ray manifestations, 88% had surfactant therapy (no further surfactant details provided). They defined this group further into mild (no oxygen dependency at 36 weeks), moderate (>21% but <30% oxygen at 36 weeks) and severe (>30% oxygen at 36 weeks) BPD. Alongside the BPD group they had data from 36 preterm subjects who did not have BPD as defined (mean GA 29±2 weeks at birth, mean birth weight 1179±408 g), 42% of whom had surfactant therapy and a term control group from local nurseries and primary schools. Vrijlandt et al. showed higher resonant frequency (f_{res}, Hz) in BPD compared preterm subjects without BPD and lower mean reactance or Xrs_{2-4}, this may reflect impaired elastic properties of the lung, possibly caused by disturbed recovery and repair after neonatal damage. Smith et al. do not recommend directly interpreting f_{res} in terms of a particular mechanical property of the respiratory system in their chapter in the European Respiratory Society Monograph. They suggest that f_{res} in respiratory disease, whether the impairment is obstructive or restrictive in the distal respiratory tract causes f_{res} to increase. Vrijlandt et al. showed no difference in respiratory resistance (Rint) between the groups, although the mean values of both preterm groups were higher compared with controls and reference values. They also showed a lower mean reactance or respiratory system compliance when comparing FOT variables for BPD vs. non-BPD subjects, but no differences using Rint.

Malmberg et al. studied a group of 49 VP/VLBW school-aged children (aged 5.3-10.7 years), 18 of whom had BPD (mean GA 26.9 [range 24.1-30.7] weeks at birth; mean birth weight 760 [range 600-1460] g), defined as the need for continuous supplemental oxygen at post conceptual age of 36 weeks, compared with 34 preterm/VLBW subjects without BPD (mean GA 28 [range 25.3-30.9] weeks at birth; mean birth weight 1100 [680-1575] g). They performed a range of lung function tests including assessments of total respiratory system resistance (Rs) and reactance using impulse oscillometry (similar to FOT), forced expiratory manoeuvres using spirometry, diffusing capacity of the lungs and lung volumes using body plethysmography.
Malmberg et al. showed that VP/VLBW subjects with BPD had increased respiratory resistance ($R_{rs}$) and reduced reactance ($X_{rs}$) compared with those VP/VLBW subjects without BPD and controls, they suggest that these results may be due to peripheral or more widespread airway obstruction.\(^{(254)}\) Malmberg et al. also showed evidence of airflow limitation ($↓FEV_1, ↓FEF_{50\%}$ and $↑R_{aw}$), air-trapping or hyperinflation ($↑RV/TLC$) and diffusion capacity impairment ($↓DL_{co}$), when comparing VP/VLBW subjects to controls, with the greatest impairments seen in those who had BPD.\(^{(254)}\)

Pelkonen et al. studied 40 VP/VLBW school-aged children (aged 7-12 years), 11 of whom had BPD, defined as requirement for supplemental oxygen at the age of 36 postconceptional weeks, compared with 20 healthy controls.\(^{(222)}\) They further stratified the preterm group based on surfactant therapy: group 1 was termed the prophylactic group where they received human surfactant 10 min of birth to infants at high risk for neonatal respiratory distress syndrome or when surfactant when respiratory failure was established ($n=17$; mean GA 27.4±1.6 weeks at birth; birth weight 1119±258 g); group 2 was defined as the rescue group and received human surfactant when established neonatal respiratory distress syndrome based on clinical, x-ray, and biochemical evidence of surfactant deficiency ($n=14$; mean GA 27.1±1.6 weeks at birth; mean birth weight 1025±316 g); group 3 consisted of those in the placebo arm in 3 different human surfactant studies ($n=9$; mean GA 27.4±1.4 weeks at birth; mean birth weight 1097±282 g).\(^{(222)}\) They performed forced expiratory flows using spirometry before and after a bronchodilator (0.5mg Terbutaline sulphate Bricanyl Turbuhaler®, Astra Draco, Lund, Sweden) and showed airflow limitation in 53% of the prophylactically treated group, in 36% of the rescue group, in 67% of the placebo group, and none of the control group.\(^{(222)}\) Pelkonen et al. reported a significance level for these results as $<0.05$ when preterm spirometry values are compared with control and $<0.001$ when the preterm subjects with BPD are compared with those without BPD, unfortunately they do not quote actual values for these differences, rather they have represented the data graphically.\(^{(222)}\) This same research group, Hakulinen et al. published data from the same group of 31 VP/VLBW school-aged children (aged 9.4±1.2 years, mean GA 28.4±2.4 weeks, mean birth weight 993±136 g), 20 of whom had BPD (aged 8.5±1.1 years, mean GA 27.8±1.4 weeks, mean birth weight 952±162 g) compared with 20 controls (aged 8.6±1.1 years, no details of their GA or birth weight were reported) who were “children of staff”. They performed forced expiratory flows using spirometry, lung volume and airways resistance measures using body plethysmography and diffusion capacity to look at the diffusive properties of the lung.\(^{(216)}\) Hakulinen et al. showed significant airflow limitation in VP/VLBW subjects regardless of BPD status compared with control and significantly reduced diffusion capacity in VP/VLBW subjects regardless of BPD status compared with control.\(^{(216)}\)
Santuz et al. studied 12 VP/LBW school-aged children (aged 8.1±1.8 years) with BPD (mean GA 30±2 weeks at birth; mean birth weight 1400±335 g), defined as requirement for supplemental O₂ at 28 days postnatal life with persistent abnormalities on chest x-ray, compared with 16 controls who were matched for age, height, weight, and level of physical activity.(255) They performed forced expiratory manoeuvres using spirometry and showed reduced lung function in BPD subjects, they also demonstrated a reduction in FEV₁ after exercise, which may indicate increased airway hyper-reactivity.(255)

Chan et al. studied 134 LBW school-aged children (aged 7.00±0.16 years).(221,244) They subdivided the VLBW group into four clinical subgroups based on the level of O₂ and/or ventilation required; 68 where described as having “no illness” had a median GA 33 (range, 28-39) weeks and median birth weight of 1700 (range, 800-1990) g, those who received “O₂ only” (n=25) had a median GA 32 (range, 27-35) weeks and median birth weight of 1430 (range, 900-1980) g, the third group received mechanical ventilation (n=27) had a median GA 30 (range, 27-34) weeks and median birth weight 1340 (range, 730-1980) g and the final group defined as “O₂ dependence” (n=10), had a median GA 28 (range, 27-32) weeks and median birth weight 1101 (range, 790-1390).(221,244) No further description is given of these clinical subgroups, although there is reference to a previous article by the same group describing respiratory symptoms in this same cohort.(256) There is no mention of BPD or surfactant.(221,244) They performed forced expiratory manoeuvres using spirometry and found reductions in variables reflecting airflow.(221,244)

Gross et al. tested 96 VLBW school-aged children (aged 7 years, mean GA 28.2±2.1 weeks at birth, mean birth weight 1173±345 g), 43 of whom had BPD, defined as a requirement for supplemental O₂ at 35 weeks’ postconceptional age.(204) No infant in this study received exogenous surfactant.(204) They performed forced expiratory manoeuvres using spirometry and showed significant airflow limitation in VLBW subjects with BPD compared with controls (FEV₁; FEF₂₅₋₇₅%; FVC).(204) They reported results for lung volume measured by nitrogen washout and showed an increased residual volume, suggestive of gas trapping.(204)

Mitchell et al. followed up 20 VP/VLBW school-aged children (aged 7±1 years; mean GA 31±3 weeks at birth; mean birth weight 1421±411 grams), 10 of whom had BPD (mean GA 30±5 at birth; mean birth weight 1359±1041 g), defined as history of neonatal respiratory distress, exposure to mechanical ventilation, radiographic features of BPD(128) and requirement on supplemental O₂ at 4 weeks of postnatal age or older compared with 10 control subjects who were healthy children of the departmental or laboratory staff members.(223) The authors make no mention of surfactant therapy although the preterm subjects were born in the pre-surfactant era (1985-1987).(223) They performed forced expiratory manoeuvres using spirometry and the diffusive properties of the lung using the diffusion capacity for carbon monoxide (DLCO) and
acetylene ($\text{D}_{\text{C}2\text{H}2}$). Carbon monoxide is mostly diffusion limited because of its high affinity to haemoglobin and acetylene is mostly perfusion limited because it is highly soluble in plasma. Mitchell et al. showed reduced DLCO in BPD subjects compared with those without BPD and control subjects, and no difference when this was corrected for alveolar volume and a reduced $\text{D}_{\text{C}2\text{H}2}$ in BPD subjects compared with those who did not have BPD and controls, suggesting that any diffusion limitation may relate to reduced cardiac output.

Korhonen et al. studied 68 VP/VLBW school-aged children (aged 7-8 years), stratified into two groups defined as requirement of supplemental $\text{O}_2$ and chest X-ray findings typical of BPD at 28 days postnatal age (BPD; n=34 [41% surfactant]; mean GA 27±2 weeks at birth; mean birth weight 951±207 g; and at 36 week corrected gestational age (sBPD; n=14 [29% surfactant]; mean GA 28±2 weeks at birth; mean birth weight 893±225 g) compared with VP/VLBW subjects without BPD (n=34 [24% surfactant] mean GA 29±2 weeks at birth; mean birth weight 1132±235 g) and a control group of next-born term children (n=34) from the same hospital. Surfactant was administered as rescue therapy for neonates with respiratory distress syndrome. They performed forced expiratory manoeuvres using spirometry, lung volume measures using body plethysmography and diffusing capacity using DLCO. Korhonen et al. showed significant airflow limitation, possible gas-trapping (↑RV/TLC) reduced diffusing capacity of the lung in those who had BPD compared those who did not have BPD and control.

Pianosi et al. assessed 32 VP/LBW school-aged children (aged 8.2-8.8 years), 17 of whom had BPD, defined as requirement for supplemental $\text{O}_2$ on the 28th postnatal and for more than 21 of 28 first days of life alongside compatible chest x-ray abnormalities at 28 postnatal days. No mention is made concerning surfactant therapy, although the infants were recruited in 1986-1987, therefore it can be assumed in this era they did not receive surfactant therapy. They performed forced expiratory manoeuvres using spirometry, lung volume measures using bodyplethysmography and diffusive properties of the lung using diffusing capacity of the lung for carbon monoxide. They found no statistically significant airflow limitation, did not report the lung volume data in this publication, and showed reduced diffusion capacity within those preterm subjects who had BPD, although well within normal limits.

Doyle et al. followed-up 240 EP/ELBW school-age children (aged 8.7±0.3, mean GA 26.7±1.9 weeks at birth, mean birth weight 885±159g), 89 of whom had BPD, defined as clinical signs of respiratory distress with an oxygen requirement at 36 weeks of postmenstrual age, compared with randomly selected controls followed from birth and matched with the EP/ELBW cohort for gender, mother’s health insurance status, and country of birth, and were randomly selected from those eligible born on the date that an ELBW/very preterm survivor was expected to be born. These data are from the cohort reported later in this thesis when they were followed up at 8-9 years of age. Exogenous surfactant was initially used as rescue therapy in...
1991, in Victoria, Australia, and limited to those subject who had established lung disease who needed assisted ventilation supplemental O₂ (FiO₂ > 0.5), in 1992 it was used more liberally, but still as rescue therapy rather than prophylaxis at birth. They performed forced expiratory manoeuvres using spirometry and lung volume measures using body plethysmography. Doyle et al. showed airflow limitation and evidence of air-trapping suggestive of hyperinflation in EP/ELBW subjects compared with controls, this impairment was worse in those who had BPD, and showed no influence from surfactant therapy. Doyle et al. showed airflow limitation and evidence of air-trapping suggestive of hyperinflation in EP/ELBW subjects compared with controls, this impairment was worse in those who had BPD, and showed no influence from surfactant therapy.

Hakulinen et al. followed 31 preterm/VLBW school-aged children, 20 of whom had BPD (mean age 8.5±1.1 years, mean GA 27.8±1.4 weeks at birth, defined as a requirement for mechanical ventilation in the first week of life (≥ 3 days), clinical signs of respiratory disease (>30 days), supplemental O₂ (>1 month of age) and ongoing changes on chest x-ray at 1 month of age, compared with a control group made up of healthy children of staff of the same age born at term. They performed forced expiratory manoeuvres using spirometry, lung volume and airways resistance measures using body plethysmography and diffusing capacity using DLCO. Hakulinen et al. showed impairment in variables reflecting airflow, no mention was made of airways resistance and the diffusing capacity of the lung was reduced in preterm subjects, this impairment were similar in those subjects with BPD.

Jacob et al. tested 15 VP/VLBW subjects without BPD (mean age 11.2±1.5 years, mean GA 28.5±2.6 weeks at birth, mean birth weight 1044.0±262.9 g) compared with 15 VP/VLBW subjects who had BPD, defined as having a clinical and x-ray based diagnosis of BPD and a requirement for supplemental O₂ (≥ 44 weeks’ post conceptual age) and who were discharged home on supplemental O₂. The authors did not mention other details regarding the recruitment of controls. They performed forced expiratory manoeuvres using spirometry, lung volume measures using body plethysmography and diffusing capacity using DLCO. Jacob et al. reported airflow impairment, increased residual volume, suggestive of air-trapping and hyperinflation, reduced diffusing capacity of the lung in VP/VLBW subjects who had BPD compared with those who did not.

Kennedy et al. reported data from a study where 102 VP/VLBW school-aged children (mean age 11.3±0.8 years, mean GA 29.6±2.8 weeks at birth, mean birth weight 1160.1±227.1 g), 26 of whom had BPD, defined following mechanical ventilation in the first week of life, supplemental O₂ required ≥ 1 month postnatal life, plus respiratory distress and x-ray changes consistent with BPD. The subjects in the study were born from 1981 to 1982, therefore would not have been exposed to surfactant therapy. They performed forced expiratory manoeuvres using spirometry, lung volume measures using body plethysmography. Kennedy et al. showed small but significant impairments in airflow and gas trapping/hyperinflation within the lungs of the preterm survivors, airflow limitation was worse in those who had BPD.
Fawke et al. followed up 182 EP/ELBW school-aged children (mean age 10.9±0.38 years, mean GA 25.0±0.7 weeks at birth, mean birth weight 750±120 g, 129 of whom had BPD (mean age 11.0±0.4 years, mean GA 24.9±0.8 weeks at birth, mean birth weight 740±120 g), defined as requirement for supplemental O₂ at 36 weeks’ postmenstrual age compared with classmates who were considered controls. (219) Eighty-five percent of the EP/ELBW subjects received surfactant. (219) They reported forced expiratory manoeuvres using spirometry before and after a bronchodilator (200 mcg salbutamol via a spacer) and showed significantly lower baseline spirometry values compared with controls, with the most significant reduction seen in those who had BPD. (219) Fawke et al. also reported increased rates of EP/ELBW subjects with clinically significant reductions in baseline lung function, especially in those who had BPD. (219) All groups had statistically significant increases in FEV₁ after bronchodilator, especially in EP/ELBW subjects and most marked in EP/ELBW subjects who had BPD. (219)

Kilbride et al. published data on 50 EP/ELBW adolescent children, aged 11.3±1.6 years (mean GA 26.1±1.6 weeks at birth; mean birth weight 701±80 g), 16 (32%) of whom had BPD defined as supplemental O₂ requirement > 36 weeks’ postmenstrual age, compared with 25 controls (NBW, >37 weeks’ GA and birth weight >2500 g). (260) This cohort was born in the pre-surfactant era. (260) They performed forced expiratory manoeuvres using spirometry and showed significant airflow limitation in EP/ELBW subjects with BPD compared with EP/ELBW subjects without BPD and NBW controls. (260)

Anand et al. followed up 128 preterm/VLBW adolescents at 15 years of age (mean GA 30.7±2.7 weeks at birth; mean birth weight 1249±185.2 g), 8 of whom had BPD, defined as requirement for supplemental O₂ for more than 28 days. (214) A comparison group (n=128, mean birth weight 3338±507.6 g) was recruited when this cohort were followed up at 8 years of age from the same school as each preterm/VLBW subjects, matched for age and gender. (214) No mention was made of surfactant; this cohort was recruited during 1980 and 1981 before surfactant therapy was introduced. (214) The mothers were asked to complete a question where smoking rates were obtained, 45.3% of mothers in the preterm/VLBW and 40.6% of mothers in the control group admitted smoking during pregnancy, these rates a higher than in Australia. (76) They performed forced expiratory flow manoeuvres using spirometry and showed a significant airflow obstruction when comparing VLBW subjects to controls and within the VLBW group comparing subjects who had BPD with those who did not. (214)

Halvorsen et al. studied 46 EP/ELBW adolescents at a mean age of 17.7±1.2 years (mean GA 27.3±1.4 weeks at birth, mean birth weight 1014±195g), 36 of who had BPD. They stratified the severity of BPD according to requirement for supplemental O₂ ≥28 days (mild BPD, n=24) and ≥36 weeks’ postmenstrual age (moderate/severe BPD, n=12), compared with 46 controls (mean birth weight 3441±311 g), selected as “the temporarily nearest term-born of the same
gender". Surfactant was not used in the era this cohort was recruited (1982-1985). Halvorsen et al. showed airflow limitation in EP/ELBW subjects compared with control, and the reduction in FEV₁ was greater with more severe BPD, but no significant bronchodilator response. They also showed evidence of increased airways resistance in EP/ELBW subjects compared with controls, the airways resistance increased with increasing BPD severity. Halvorsen et al. also performed an airway challenge, using methacholine to induce airway obstruction.

Northway et al. followed up 26 preterm/LBW young adults with BPD (mean age 18.3±2.7, mean GA 33.2±3.8 weeks at birth, mean birth weight 1894±703 g [4 subjects in this group had birth weights > 2500 g]), defined as a requirement for supplemental O₂ and changes on chest x-ray at 1 month consistent with BPD. They also recruited 26 of who did not have BPD (mean age 18.8±2.7 years, mean GA 34.5±3.6 weeks at birth, mean birth weight 1978±809 g [5 subjects in this group had birth weights > 2500 g]), did not receive mechanical ventilation born at the same medical centre who lived nearby and were matched for birth weight and gender of those subjects who had BPD. A third group of 53 normal term subjects of the same age were also studied. These subjects were recruited between 1964 and 1973, well before surfactant therapy was introduced. They performed forced expiratory flow manoeuvres, diffusion capacity of the lungs using DLCO also airways resistance measured by body plethysmography. They also performed a single breath nitrogen washout as a measure of closing volume, i.e. the lung volume where the small airways begin to close. Northway et al. showed airway obstruction increased airways resistance, hyperinflation (↑ RV/TLC) and higher closing volume in those subjects with BPD compared with those without BPD and the normal control group.

No serial data have been published for lung function in preterm adults, whether or not they had BPD. Lung function abnormalities that may persist into adulthood include airway hyper-reactivity and persistent airflow obstruction.

Doyle et al. studied 63 preterm ELBW (birth weight 500 to 999 g), 124 preterm VLBW (birth weight 1000 to 1500 g), 33 of whom had BPD, defined as requirement for assisted ventilation, had respiratory distress and needed supplemental O₂ with and abnormal chest x-ray ≥28 days consistent with Northway’s stage 3 or 4 BPD, compared with 60 controls (birth weight >2499 g). Those without BPD had a mean GA of 26.8±1.6 weeks at birth and mean birth weight of 909±176 g; the non-BPD group had a mean of GA 29.3±1.8 weeks at birth and a mean birth weight 1150±221 g. These groups were recruited during 1977 and 1982, before surfactant therapy had been introduced. They performed forced expiratory flow manoeuvres using spirometry and lung volumes measured by body plethysmography at 19.4±1.3 years.
Doyle et al. showed airflow limitation in the preterm/VLBW groups, most evident in those who had BPD and no differences in lung volumes.\(^{(187)}\)

Vrijlandt et al. studied 42 preterm/LBW young adults aged 19±0.3 years (mean GA 30±2 weeks at birth, mean birth weight 1246±232 g), 9 of whom had BPD, defined as requirement for O\(_2\) > 28 days and chronic chest x-ray abnormalities.\(^{(80)}\) None of the study subjects received exogenous surfactant. They performed forced expiratory manoeuvres using spirometry, lung volume and airways resistance measures using body plethysmography and diffusing capacity using DL\(_{CO}\).\(^{(80)}\) They showed significant reductions in variables reflecting airflow, increased airways resistance, a slight increase in RV/TLC that may not be clinically significant, and a reduction in the diffusion capacity of the lungs in preterm/LBW subjects compared with control.\(^{(80)}\) Interestingly they report BPD has no association with the impairments they have reported in lung function, although they only included male subjects in the analysis.\(^{(80)}\)

Narang et al. published data from a study where they followed up 60 LBW (mean age, but not exclusively preterm adults aged 21.7 (range, 20.5-22.9) years, 7 of whom had BPD, defined as requirement for supplemental O\(_2\) at greater than 28 days’ postnatal age, compared with 50 controls (<26 years, birth weight > 2000 g, GA ≥ 37 weeks at birth).\(^{(261)}\) The subjects were born in the pre-surfactant era.\(^{(261)}\) They performed forced expiratory manoeuvres using spirometry and showed no difference in airflow variables between the LBW subjects compared with control.\(^{(261)}\)

In summary, from the data available for very low and extremely low birth weight and very or extremely preterm infants and pre-school children, particularly those who had BPD, have persistent reductions in airflow and higher airways resistance compared with those who did not have BPD, and compared with control subjects.\(^{(3,23,220,227,234,241,246-251,253)}\)

Some of the studies in Table 4 pre-date the widespread use of surfactant into clinical practice, with cohorts born before 1990, whereas other studies comprise subjects born in recent years, when surfactant therapy was freely available. Some are regional cohorts, with the intention of assessing as many survivors as possible from a defined geographical region, this reduces selection biases and hence makes any results more widely applicable. Other studies are highly selective, sharing characteristics for example having been ventilated or having had BPD in the newborn period. The applicability of the results from these latter studies to all preterm survivors is less clear than for complete geographical cohorts. Other characteristics of those selected for study, such as birth weight or gestational age, also vary widely.

The numbers of preterm subjects in individual studies vary from as few as 4 to as high as 240. Some researchers have reported results as actual values (mLs or L), % predicted for age,
height and sex; others have reported results as z-scores for age, height and sex. Regardless of the basis for the results, if mean, SD and sample size have been reported for both groups, it is possible to pool the data and calculate overall standardized mean differences and 95% confidence intervals, contrasting preterm survivors with controls.

Most individual studies have reported significant reductions in FEV₁ in preterm subjects compared with controls (Table 3). The results are mostly consistent, regardless of the differences in the demographic characteristics and other features between the various studies, including whether the cohorts were born before or after surfactant was available. The largest difference between preterm and term-born subjects from the surfactant era was from the regional study that included only survivors born <26 weeks’ gestation, with the standardized mean difference of -1.26 SD between groups.(219) There were no obvious trends over time within either subgroup, with the studies ordered by increasing years of birth of the subjects.

Several of the studies reported results from the same cohort, but at different ages. Doyle et al. report mean standardized differences in FEV₁ between preterm subjects and controls at 14, 18 and 25-28 years of age that remain relatively stable.(187,239) In contrast, Vollsaeter et al. who reported on survivors <1001 g birth weight or <29 weeks’ gestational age from a regional cohort in Norway, results between 17 and 25 years for subjects born in 1982-85, and between 10 and 17 years for subjects born in 1991-92 showed an improvement over time.(262) Several of the studies reported results from similar subjects born within the same region, but in different eras, with little evidence for a substantial change over time.(186,262,263)

Within preterm groups, those who had BPD in the newborn period had greater reductions in FEV₁ compared with those who did not have BPD in most individual studies, The reductions with BPD were larger in the presurfactant era than in the surfactant era. There were no obvious trends with time in either subgroup.(186,187,204,212,216,217,219,238,254,257,259-263)

Several of the studies, in Table 3 reported FEV₁ results from similar subjects born within the same region, but in different eras, with some evidence of change over time.(186,262,263)

In addition to changes in the FEV₁, there are several studies that report changes in other variables consistent with airflow obstruction in the smaller airways (reduced FEF₂₅₋₇₅%) and air trapping (raised RV/TLC) in very preterm survivors, especially in those who had BPD.(219,262) In addition to overall reductions in airflow variables, very preterm survivors have higher proportions with values in clinically important ranges; Fawke and colleagues reported that 32% of the subjects born <26 weeks’ gestational age and 66% of those with BPD had results that were clinically important.(219) Despite having more abnormal lung function on average and higher proportions with values in clinically important ranges, most very preterm survivors are asymptomatic.

However with the expected decline in lung function with ageing from the mid-20s onwards, it is
anticipated that disproportionately more preterm survivors than controls will present with symptoms of chronic obstructive airways disease as they grow older, particularly those who survived with BPD.

Several studies have shown preterm subjects; especially those with BPD have reduced diffusion capacity within their lungs from infancy through childhood and young adulthood.\(^8\) There is evidence that preterm subjects have increased airway reactivity compared to controls, in addition to obstruction. In these studies preterm subjects showed increased bronchoconstriction when exposed to methacholine and histamine airway challenges and increased bronchodilator response, especially in those with BPD.\(^{39, 53, 62, 63}\) Airflow impairment seen in preterm cohorts may be associated with this increased airway reactivity. Impaired diffusion and air trapping within the lungs also occur more frequently in preterm survivors compared with controls, and the impairment continues into early adulthood.\(^{238, 264}\)\(^{246}\)
Table 4: Selected cross-sectional lung function data from studies of ELBW/preterm survivors, including some with BPD.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Age (mean±SD)</th>
<th>Participants</th>
<th>GA (weeks)</th>
<th>BW (grams)</th>
<th>PFT</th>
<th>Results (mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hilgendorff et al.</td>
<td>38 (range, 32-44) weeks</td>
<td>VP/VLBW BPD 23</td>
<td>26 (range, 24-30) wk</td>
<td>1040 (range, 500-1730) g</td>
<td>LV, Raw</td>
<td>↓ FRC VP/VLBW FRC 16.3±4.0 vs. FRC normal values 19.6±3.4 mL.kg⁻¹, p&lt;0.01</td>
</tr>
<tr>
<td>(Not specified)(247)</td>
<td></td>
<td>VP/VLBW No BPD 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hofhuis et al. (1998-1999)</td>
<td>6.2±0.9 months corrected</td>
<td>ELBW PREM BPD 22</td>
<td>26.9 wk±1.7 wk</td>
<td>826 g±156 g</td>
<td>VmaxFRC</td>
<td>↓ VmaxFRC in conventional mechanical ventilation (CMV) group compared with HFOV group (CMV -2.5 [±0.1] z-score vs. HFOV -1.9 [±0.2] z-score)</td>
</tr>
<tr>
<td></td>
<td>12.6±1.1 months corrected</td>
<td></td>
<td>26.6 wk±1.7 wk</td>
<td>852 g±156 g</td>
<td>FRC</td>
<td></td>
</tr>
<tr>
<td>Sanchez-Solis et al.</td>
<td>7.5±5.7 months</td>
<td>VLBW PREM BPD 43 (19 mild; 15 moderate; 9 severe BPD)</td>
<td>26.7 wk±1.7 wk</td>
<td>zBW 0.06±1.0</td>
<td>RVRTC</td>
<td>↓ FEF0.5 (BPD -1.57±0.7 vs. No BPD -1.05±1.1 z-score; p=0.02)</td>
</tr>
<tr>
<td>(Not specified)(248)</td>
<td>6.3±6.3 months</td>
<td>VLBW PREM No BPD 32</td>
<td>29.6 wk±2.0 wk</td>
<td>zBW -0.12±1.4</td>
<td></td>
<td>↓ FEF25-75% (BPD -2.46±0.7 vs. No BPD -1.68±1.3 z-score; p=0.001)</td>
</tr>
<tr>
<td>Balinotti et al.</td>
<td>11.6±3.8 months</td>
<td>ELBW PREM BPD 39 Controls 61</td>
<td>26wk±1.7 wk</td>
<td>870g±240g</td>
<td>DLCO, VA</td>
<td>↓ DLCO (BPD 2.88 mL.min.mmHg⁻¹ vs. NBW 3.23 mL.min.mmHg⁻¹; p=0.0004)</td>
</tr>
<tr>
<td>(2007-2009)(3,249)</td>
<td></td>
<td></td>
<td>25.6wk±1.7wk</td>
<td>767g±200g</td>
<td>DLCO/VA</td>
<td>↓ DLCO/VA (BPD 2.7 mL.min.mmHg⁻¹ vs. NBW 3.4 mL.min.mmHg⁻¹; p&lt;0.0001)</td>
</tr>
<tr>
<td>Fakhoury et al.</td>
<td>8-34 months</td>
<td>ELBW PREM BPD 44</td>
<td>28.1wk±2.5wk</td>
<td>1100g±420g</td>
<td>VmaxFRC</td>
<td>↓ VmaxFRC (-1.92 [±1.04]; -1.79 [±1.5]; -1.67 [±1.5] z-scores at 6, 12 and 24 months post-discharge respectively</td>
</tr>
<tr>
<td>(1999-2003)(241)</td>
<td></td>
<td></td>
<td>27.9wk±2.4wk</td>
<td>1020g±400g</td>
<td>FRC</td>
<td></td>
</tr>
<tr>
<td>Latzin et al.</td>
<td>40-54 months</td>
<td>VLBW PREM Mild BPD</td>
<td>28.4wk±2.1wk</td>
<td>870g±290g</td>
<td>LCI</td>
<td>↑ Respiratory rate with ↑ BPD severity</td>
</tr>
<tr>
<td>(1999-2007)(250)</td>
<td></td>
<td>VLBW PREM Moderate BPD</td>
<td></td>
<td></td>
<td>Vt</td>
<td></td>
</tr>
<tr>
<td>Elsbew PREM Severe BPD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robin et al.</td>
<td>68.0±35.6 months</td>
<td>VLBW PREM BPD 28</td>
<td>26.4±2.1wk</td>
<td>898g±353g</td>
<td>VmaxFRC</td>
<td>↓ FEV0.5 (76.3±19.6% pred vs. NBW 99.7±18.3% pred; p&lt;0.001)</td>
</tr>
<tr>
<td>(Not specified)(234)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LV</td>
<td>↓ FEF25-75% (74.0±26.8% pred vs. NBW 95.0±18.7% pred; p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑ FRCpleth (107.9±25.3% pred vs. NBW 95.9±14.8% pred; p=0.052)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑ RV (124.5±42.7% pred vs. NBW83.9±22.7%;pred; p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑ RV/TLC (128.2±35.3% pred vs. NBW 85.6±19.0; p&lt;0.001)</td>
</tr>
<tr>
<td><strong>Schmalish et al. (1995-2010)</strong>(251)</td>
<td>50, 70 and 100 weeks</td>
<td>VLBW PREM BPD 29</td>
<td>26.4 wk±2.2 wk 816 g±243 g 29.1 wk±2.1 wk 1124 g±248 g</td>
<td>Vt VmaxFRC Rs FRCpleth FRCsr6</td>
<td>No significant differences in any lung function variable</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td><strong>Hülskamp et al. (Not specified)</strong>(227)</td>
<td>39 to 47 weeks</td>
<td>VP/VLBW BPD</td>
<td>26.6 wk±2.1 wk 890 g±290 g</td>
<td>FRC LCI Vt</td>
<td>↓FRC (-0.47 mL/↓gestational week, p=0.03; -1.94 mL/↓birth weight z-score, p=0.009; -0.04 mL/↑day of supplemental oxygen)</td>
<td></td>
</tr>
<tr>
<td><strong>Talmaciu et al. (1995-1997)</strong>(253)</td>
<td>30.2±6.5 months</td>
<td>VP O$_2$ dependent 21</td>
<td>26.9±2.3 wk BW not specified 26.1±1.9 wk BW not specified</td>
<td>VmaxFRC FRCN2 VT</td>
<td>↓VmaxFRC/FRC (BPD 0.34±0.21 sec$^{-1}$ vs. BPD Non O$_2$/control 0.81±0.40 sec$^{-1}$, p=0.003)</td>
<td></td>
</tr>
<tr>
<td><strong>Kairamkonda et al. (Not specified)</strong>(220)</td>
<td>46 (38.0-54.5) months</td>
<td>VLBW VP BPD 28</td>
<td>27(IQR, 26-28) wk 995(IQR, 827-1151) g 29(IQR, 28-31) wk 1366(IQR, 1243-1672) g</td>
<td>Rint</td>
<td>↑Rint (BPD 1.42 [0.73 - 2.04] z-score vs. No BPD 1.00[0.38 – 1.23] z-score)</td>
<td></td>
</tr>
<tr>
<td><strong>Vrijlandt et al. (1998-2001)</strong>(246)</td>
<td>3-5 years</td>
<td>VP/VLBW BPD 41</td>
<td>28±2 wk 1051±536 g 29±2 wk 1179±408 g &gt;37 wk &gt;2500 g</td>
<td>FOT Rint</td>
<td>↑Rint (BPD 9.9±2.5 hPa.s.L$^{-1}$ vs. control 7.6±2.4 hPa.s.L$^{-1}$, p&lt;0.001; No BPD 9.3±2.9 hPa.s.L$^{-1}$ vs. control, p=0.003) ↑Rint 24 (BPD 7.3±2.0 hPa.s.L$^{-1}$ vs. control 6.2±1.9 hPa.s.L$^{-1}$, p=0.009; No BPD 7.1±1.7 hPa.s.L$^{-1}$ vs. control, p=0.02) ↓Xrs 24 (BPD -3.0±1.5 hPa.s.L$^{-1}$ vs. No BPD -1.95±1.6 hPa.s.L$^{-1}$, p=0.008; BPD vs. control -1.25±0.9 hPa.s.L$^{-1}$, p&lt;0.001; No BPD vs. control, p=0.02) ↑fres (BPD 26.8±5.9 Hz vs. No BPD 22.7±4.0 Hz, p=0.001; BPD vs. control 22.7±5.0 Hz, p=0.001) ↑Rint (BPD 1.06±0.37 kPa.s.L$^{-1}$ vs. control 0.70±0.21 kPa.s.L$^{-1}$, p&lt;0.001; No BPD 0.91±0.28 kPa.s.L$^{-1}$ vs. control, p=0.001)</td>
<td></td>
</tr>
</tbody>
</table>
| **Malmberg et al. (1989-1991)**(254) | 5.3 to 10.7 years | VP/VLBW BPD 15 | 26.9 (range, 24.1-30.7) wk 760 (range, 600-1460)g | FOT SP, LV, DLCO | ↑RsS (BPD 1.90±1.55 z-score vs. No BPD 1.08±1.07 z-score vs. control -0.02±0.91) ↓XrsS (BPD -2.29±1.53 z-score vs. No BPD -0.29±1.08 z-score vs.
<table>
<thead>
<tr>
<th>Study</th>
<th>Age</th>
<th>BPD/Control</th>
<th>GA/BW</th>
<th>FEV₁ (pred)</th>
<th>FEF 25-75% (pred)</th>
<th>DLCO (pred)</th>
<th>RV/TLC (pred)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelkonen et al. (1983-1987) [216,222]</td>
<td>9.8 (range, 8.0-10.7) years</td>
<td>VP/VLBW No BPD 34</td>
<td>27.4±1.6 wk 1119±258 g</td>
<td>SP LV DLCO</td>
<td>↓FEV₁ (BPD 88 ±13% vs. control 99 ±18% pred, p=0.017)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8.4 (range, 7.4-11.7) years</td>
<td>VP/VLBW Control 18</td>
<td>27.1±1.6 wk 1025±316 g 1097±282 g</td>
<td>GA not specified BW not specified</td>
<td>↓FEF₂₅-₇₅% (BPD 77 ±16% vs. control 109 ±6% pred, p=0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Santuz et al. (1981-1987) [255]</td>
<td>8.1±1.8 years</td>
<td>PREM/LBW BPD 12</td>
<td>30±2 wk 1400±335 g</td>
<td>SP LV</td>
<td>↓FEV₁ (BPD 83 ±13% vs. control 100 ±8% pred)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chan et al. (1979-1980) [221,244]</td>
<td>7 (0.16) years</td>
<td>LBW 134</td>
<td>GA not specified BW &gt;2000 g</td>
<td>SP</td>
<td>↓FEV₀.₇₅ (1.16 [0.19] L vs. control 1.25 [0.17] L; p&lt;0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gross et al. (1985-1986) [204]</td>
<td>7 years</td>
<td>VLBW PREM BPD 43</td>
<td>All PREM 28.2±2.1 wk All PREM 1173±345 g</td>
<td>SP LV</td>
<td>↓FEV₁ (BPD 83 ±17 % vs. No BPD 98 ±18 % pred; p&lt;0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>VLBW PREM 53</td>
<td>GA 38-42 wk</td>
<td>BW not specified</td>
<td>↓FVC (BPD 66 ±24 % vs. No BPD 84 ±27 % pred; p&lt;0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitchell et al. (1985-1987) [223]</td>
<td>7±1 years</td>
<td>VP/VLBW BPD 10</td>
<td>30±5 wk 1359±1041 g</td>
<td>SP, DLCO, DLCO₂, DLCO₂H₂</td>
<td>↓DLCO (BPD 9.16±1.32 mL/min/mmHg vs. control 15.29±1.61 mL/min/mmHg, p&lt;0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Age Range</td>
<td>Controls</td>
<td>VP/VLBW BPD</td>
<td>VP/VLBW No BPD</td>
<td>SP, LV, DLCO</td>
<td>FEV1</td>
<td>FEF25</td>
</tr>
<tr>
<td>------------------------------</td>
<td>-----------</td>
<td>----------</td>
<td>-------------</td>
<td>----------------</td>
<td>--------------</td>
<td>------</td>
<td>-------</td>
</tr>
<tr>
<td>Korhonen et al. (1990-1994)</td>
<td>7-8 yrs</td>
<td>10</td>
<td>10</td>
<td>31±3 wk</td>
<td>31±3 wk</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1421±411 g</td>
<td>1421±411 g</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40±1 wk</td>
<td>40±1 wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3157±606 g</td>
<td>3157±606 g</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>31±3 wk</td>
<td>27±2 wk</td>
<td>27±2 wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1132±235 g</td>
<td>1132±235 g</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>28±2 wk</td>
<td>989±225 g</td>
<td>989±225 g</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>29±2 wk</td>
<td>29±2 wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1132±235 g</td>
<td>1132±235 g</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40±1 wk</td>
<td>40±1 wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3597±498 g</td>
<td>3597±498 g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pianosi et al. (1986-1987)</td>
<td>8.2-8.8y</td>
<td>34</td>
<td>17</td>
<td>27.9 wk no SD</td>
<td>27.9 wk no SD</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BW not specified</td>
<td>BW not specified</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>885g (159g)</td>
<td>885g (159g)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doyle et al. (1991 to 1992)</td>
<td>8.7 (0.3)</td>
<td>208</td>
<td>240</td>
<td>26.7wk (1.9wk)</td>
<td>26.7wk</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>Hakulinen et al. (1978-1985)</td>
<td>8.5±1.1y</td>
<td>20</td>
<td>20</td>
<td>27.8±1.4 wk</td>
<td>27.8±1.4 wk</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>952±162 g</td>
<td>952±162 g</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>28.4±2.4 wk</td>
<td>28.4±2.4 wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>992±136 g</td>
<td>992±136 g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jacob et al. (1981 to 1987)</td>
<td>10.6±1.7</td>
<td>15</td>
<td>15</td>
<td>28.7±2.1 wk</td>
<td>28.7±2.1 wk</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1110±328 g</td>
<td>1110±328 g</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>28.5±2.6 wk</td>
<td>28.5±2.6 wk</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** SD = Standard Deviation; VP/VLBW = Very Preterm/Very Low Birth Weight; BPD = Bronchopulmonary Dysplasia; Controls; DLCO = Diffusing Capacity of the Lung for Carbon Monoxide; SP = Single Phase; LV = Lung Volume; DL = Diffusing Capacity; FEF = Forced Expiratory Flow; FEV1 = Forced Expiratory Volume in One Second; FVC = Forced Vital Capacity; RV = Residual Volume; TLC = Total Lung Capacity; range = range of values; %pred = percent of predicted value; p<0.05 = p-value of less than 0.05; p<0.01 = p-value of less than 0.01; p<0.001 = p-value of less than 0.001.
| Study                                      | Follow-up | Age Range | VLBW/ELBW | ELBW | Controls | Preterm/VLBW | Preterm/VLBW Controls | Preterm/VLBW Controls ELBW | Preterm/VLBW Controls ELBW Controls | Preterm/VLBW Controls ELBW Controls Controls | Preterm/VLBW Controls ELBW Controls Controls Controls | Preterm/VLBW Controls ELBW Controls Controls Controls Controls | Preterm/VLBW Controls ELBW Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Controls Control
<table>
<thead>
<tr>
<th>Study</th>
<th>Participant Details</th>
<th>SEV 1/FVC Decrease</th>
<th>FEV1/FVC Decrease</th>
<th>FEV1/FVC Decrease</th>
<th>FEV1/FVC Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halvorsen et al. (1982-1985) [240]</td>
<td>PREM Mild BPD 24; PREM Moderate/severe BPD 12; PREM No BPD 10; Controls 46</td>
<td>3338±507.6 g</td>
<td>↓FEV1/FVC (VLBW 87.0±9.0 %pred vs. Control 90.8±6.4 %pred, p&lt;0.001)</td>
<td>↓FEV1/FVC (BPD 57.5±25.7 %pred vs. No BPD 75.8 %pred, p&lt;0.001)</td>
<td>↓FEV1/FVC (Mod/severe BPD 87.8±13.8 %pred vs. Mild BPD 96.1±12.1 %pred vs. No BPD 101.8±14.6 %pred vs. control 108.1 %pred, p=0.02)</td>
</tr>
<tr>
<td>Northway et al. (1963 to 1973) [238]</td>
<td>PREM BPD 26; PREM No BPD 26; Control 53</td>
<td>33.2±3.8 wk 1894±703 g 34.5±3.6 wk 1978±809 g GA not specified</td>
<td>↓FEV1 (BPD 74.8±2.9% pred vs. No BPD 96.6±2.0% pred [p&lt;0.0001] vs. control 100.4±1.5% pred [p&lt;0.0001])</td>
<td>↓FEV1 (BPD 74.8±2.9% pred vs. No BPD 96.6±2.0% pred [p&lt;0.0001] vs. control 100.4±1.5% pred [p&lt;0.0001])</td>
<td>↓FEV1 (BPD 74.8±2.9% pred vs. No BPD 96.6±2.0% pred [p&lt;0.0001] vs. control 100.4±1.5% pred [p&lt;0.0001])</td>
</tr>
<tr>
<td>Doyle et al. (1977 to 1982) [187]</td>
<td>VLBW BPD 33; VLBW No BPD 114; Control 37</td>
<td>26.8±1.6 wk 909±176 g 29.3±1.8 wk 1150±221 g GA not specified &gt; 2499 g</td>
<td>↓FEV1 (BPD 81.6±18.7 %pred vs. No BPD 92.9±12.8 %pred, p&lt;0.001)</td>
<td>↓FEV1 (BPD 81.6±18.7 %pred vs. No BPD 92.9±12.8 %pred, p&lt;0.001)</td>
<td>↓FEV1 (Mod/severe BPD 87.8±13.8 %pred vs. Mild BPD 96.1±12.1 %pred vs. No BPD 101.8±14.6 %pred vs. control 108.1 %pred, p=0.02)</td>
</tr>
<tr>
<td>Vrijlandt et al. (1983) [80]</td>
<td>PREM 42 (BPD=9); Control 48</td>
<td>30±2 wk 1246±232 g 37-42 wk BW not specified</td>
<td>↓FEV1 (BPD 81.6±18.7 %pred vs. No BPD 92.9±12.8 %pred, p&lt;0.001)</td>
<td>↓FEV1 (BPD 81.6±18.7 %pred vs. No BPD 92.9±12.8 %pred, p&lt;0.001)</td>
<td>↓FEV1 (BPD 81.6±18.7 %pred vs. No BPD 92.9±12.8 %pred, p&lt;0.001)</td>
</tr>
</tbody>
</table>
Narang et al. (1979-1980)(261) median 21.7 (range, 20.5-22.9) years

| LBW BPD 58 | Median 31.5 (range, 27-37) wk |
| controls 48 | Median ~1440 (range, 790-1990) g* |
| controls 48 | Median 40.0 (range, 36-43) wk |
| controls 48 | Median ~3410 (range, 2720-5800) g* |

No significant differences in any lung function variable

Values expressed as mean (SD) unless otherwise stated; * - reported as kilograms to 2 decimal places; PFT – Pulmonary function test; SP – Spirometry; LV – Lung volumes; MBW – Multiple breath washout; FEV1 – forced expiratory volume in one second; FVC – forced vital capacity; FEF25%, FEF50%, FEF75%, FEF25-75% – forced expiratory flows at 25%, 50%, 75% and from 25% to 75% of FVC; TLC – total lung capacity; RV – residual volume; FRC - functional residual capacity; FRCpleth – FRC measured by body plethysmography; FRCsulph – FRC measured by Sulphur hexafluoride inert gas washout; FRCN2 – FRC measured by Nitrogen inert gas washout; DLCO – diffusing capacity of the lung for carbon monoxide; Raw – airways resistance; Gaw – specific airways compliance; Raw – airways resistance; Gaw – specific airways compliance; Rint – Resistance interrupter technique; VmaxFRC – Infant spirometry; DEX42 – 42 day course of dexamethasone; DEX18 – 18 day course of dexamethasone(125) CMV HFOV; zBW – neonatal weight z-score; ∆N2/L – Phase III slope, closing volume by single breath nitrogen washout
5.1.6.1.3 Exercise testing

No exercise data are available in preterm or low birth weight subjects during infancy and pre-school ages, due to practical limitations of performing exercise in these age groups.

Table 5 displays exercise test results from articles reporting outcomes in preterm or low birth weight subjects, with and without BPD, compared with controls.

Kriemler et al. tested 17 school aged children who had BPD (age, range 5.8-7.8 years, mean GA 27.1±1.9 weeks’, mean birth weight 970±285 g), defined as O₂ dependency and persistent symptoms of respiratory distress in preterm infants at 28 days after delivery who had received mechanical ventilation ≥1 week and had chest x-ray features consistent with BPD, compared with 14 children who did not have BPD (mean age 6.1-7.8 years, 28.3±1.7 weeks at birth, 1108±202 g) and a control group recruited from healthy local school and kindergarten children (mean age 5.5-7.4 years, mean birth weight 3455±595 g).(265) They performed maximal cardiopulmonary exercise tests to determine maximal aerobic power using a continuous cycling test with increasing load and increments based on the child’s height, and the test went for between 6 and 10 minutes.(265) Kriemler et al. defined maximal effort during the CPX test as inability of the subject to keep pedalling at the required speed, despite continuous verbal encouragement by the researcher.(265) They showed no difference between the groups for peak mechanical power, O₂ uptake, maximal HR and respiratory exchange ratio (RER, \(V'CO_2/V'O_2\)).(265) Kriemler et al. showed alterations in ventilatory patterns at peak exercise both between preterm subjects with and without BPD and comparing premature BPD survivors with controls.(265)

Gross et al. tested 96 VP/VLBW school-aged children (aged 7 years, mean GA 28.2±2.1 weeks at birth, mean birth weight 1173±345 g), 43 of whom had BPD, defined as requirement for supplemental O₂ at 35 weeks’ postconceptional age, compared with a control group recruited from healthy term neonates matched for gender, maternal race, years of formal education and marital status (aged 7 years, mean GA 40.0±1.1 weeks at birth, mean birth weight 3565±427 g).(204) They performed a maximal cardiopulmonary exercise test with increasing load based on height and gender, according to the Bruce protocol.(204) They reported an increase in exercise induced bronchoconstriction, a lower heart rate and no difference in \(V'O_2\text{max}\) in preterm, VLBW subjects at an average age of 7 years compared with a control group.(204)

Santuz et al. recruited 12 VP/LBW school-age children (mean age 8.1±1.8 years, mean GA 30±2 weeks at birth, mean birth weight 1400±335 g) with a history of BPD, defined as chest x-ray changes including hyperinflation, multiple cystic areas and fibrotic strands at 1 month of life, compared with 16 healthy controls recruited from a local school.(255) They performed a maximal cardiopulmonary exercise test on a treadmill using a stepwise protocol where the speed is set at
6.5km.h\(^{-1}\) and treadmill elevation is increased by 2% every 2 minutes until exhaustion.(255) They considered the test to complete when 2 of the following criteria were met: 1) HR “close to the theoretical maximum”; 2) no increase in oxygen consumption despite increasing workload; 3) inability of the subject to continue with the test despite “vigorous encouragement”. Santuz et al. reported a reduced \(\dot{V}O_2\)max, reduced ventilation rate, increased respiratory rate and an increased rate of exercise induced bronchoconstriction, based on post-exercise fall in FEV\(_1\), in VP/LBW subjects at 6-12 years of age compared with control subjects.(255)

Pianosi et al. identified 17 preterm/LBW school-aged children with BPD (mean age 8.8 years, mean GA 28.3\([\text{range, 24-31}]\) weeks at birth, mean birth weight 1165\([\text{range, 770-1850}]\) g), defined as requirement for supplemental O\(_2\) for >21/28 days postnatal life and compatible chest x-ray abnormalities, and 15 preterm/LBW subjects with HMD (mean 8.5 years), compared with 15 healthy controls (mean age 8.2 years).(266) They performed a maximal cardiopulmonary exercise test on a cycle ergometer using a progressive protocol where the exercise intensity increased in step 8watts each minute.(266) Pianosi et al. considered an acceptable end of test to have occurred when the subject reached exhaustion, manifested by a falling pedalling rate and visible signs of exhaustion.(266) They also asked subjects (n=15 preterm/LBW) to perform a second exercise test on the cycle using a sub-maximal constant load protocol to enable them to measure cardiac output.(266) Pianosi et al. showed demonstrated a reduced \(\dot{V}O_2\)max and no differences in stroke volume in preterm/LBW compared with control.(266)

Barker et al. recruited subjects with birth weights <1500 g and gestational ages <37 weeks at birth who attended their neonatal intensive care unit between 1983 and 1989.(267) They tested 13 preterm/VLBW subjects without BPD (mean age, 9.8 \([\text{range, 8-14}]\) years, mean GA 30.3 \([\text{range, 28-33}]\) weeks at birth, mean birth weight 1139 \([\text{range, 710-1480}]\) g), 13 preterm/VLBW subjects with BPD, defined as “radiographic criteria at one month of age” (mean age, 10.4 \([\text{range, 8-14}]\) years, mean GA 33.5 \([\text{range, 30-36}]\) years at birth, mean birth weight 1264 \([\text{range, 900-1490}]\) g), compared with a control group of “healthy children matched for age, height and weight.(267) No further details about the control group were given.(267) They performed a non-standard exercise test on a cycle ergometer where the subject cycled at 60 rpm for approximately 25 minutes, during which time the work load altered between sub maximal and “pseudo-random binary sequence” where the work load increased and decreased, then a final “progressive ramp” where the work rate increased in increments based on subject height.(267) They determined a maximal effort was achieved when the HR was >175bpm, the respiratory exchange ratio was >1, the speed of pedal rotation decreased, and the clinical impression was the child was exhausted, as assessed by “an experienced examiner”.(267) Barker et al. showed no difference in \(\dot{V}O_2\)max comparing preterm subjects who had BPD with the BPD group and controls, but did report reduced ventilation rates, tidal volumes and work rates in the BPD subjects.(267)
Baraldi et al. recruited 15 preterm VLBW at 9.9±1.8 years (range, 7.8-12.2 years, mean GA 32.1±3.0 weeks at birth, mean birth weight 1287±143 g), none with bronchopulmonary dysplasia, and 26 controls (mean age 9.7±1.9 years). They further subdivide the preterm subjects into 2 groups based on birth weight for GA: 1, small for GA or growth restricted (SGA); 2, appropriate for GA (AGA). They performed cardiopulmonary exercise testing using a progressive treadmill protocol, where the speed was set at 6.5km.h⁻¹ and the elevation of the treadmill was increased at 2 minute intervals until exhaustion, using a Douglas bag system for gas analysis. A Douglas bag is an inflatable leather bag that allows collection of expired gases that can be analysed post-exercise; the subject traditionally wears the apparatus on their back while exercising. Baraldi et al. reported no differences in any variable when comparing preterm/VLBW subjects and no association with growth restriction or being SGA, apart from a slightly increased oxygen cost of running.

Smith et al. studied 126 VP/ELBW school-aged children (aged 10.1±1.1 years, mean GA 26.9±1.7 weeks at birth, mean birth weight 862.4±160.9 g), 37 of whom had BPD, compared with 34 control subjects (mean age 11.6±0.8 years, mean GA 39.4±1.2 weeks at birth, mean birth weight 3400.5±512.5 g). No details were provided about how BPD was defined. They performed a fitness tests using 6-minute walk and 20 metre shuttle run-test. The 6-minute walk test is used to determine the distance each subject could walk in the time period, Smith et al. found no difference between VP/ELBW and control subjects. The 20 m shuttle test is a progressive free-running test where the time allotted for the subject to complete each shuttle (20 m walk/jog/run) is decreased as the test progresses, the preterm subjects achieved significantly less shuttle stages and therefore achieved a significantly reduced distance. Smith et al. calculated \( V'O_2\text{peak} \) from the shuttle stage reached during the 20 m shuttle test, not directly from a cardiopulmonary exercise test, and therefore showed a reduction in the estimated \( V'O_2\text{peak} \) when calculated from other non-standardised forms of maximal exercise, such as a shuttle test, and a reduced heart rate in preterm, VP/ELBW subjects.

Jacob et al. tested 15 VP/VLBW subjects without BPD (mean age 11.2±1.5 years, mean GA 28.5±2.6 weeks’ at birth, mean birth weight 1044.0±262.9 g) compared with 15 VP/VLBW subject who had BPD, defined as having a clinical and x-ray based diagnosis of BPD and a requirement for supplemental \( O_2 \) (≥ 44 weeks’ post-conceptual age) and who were discharged home on supplemental \( O_2 \). The authors did not mention other details regarding the recruitment of NBW term-born controls. They performed a symptom-limited progressive exercise test on a cycle ergometer, where the exercise intensity increased each minute, based on height, gender and predicted maximal work load (Wmax) so the test would last 6-10 minutes. They showed found no difference in \( VO_2\text{max} \) but an increased use of the ventilatory or respiratory reserve in subjects who had BPD compared with controls.
Welsh et al. published data from a study of 38 EP/ELBW school-aged children (aged 11.1±0.4 years, mean GA 25.0 [IQR 24.7-25.1] weeks at birth, mean birth weight 740±107 g), 27 of whom had BPD, defined as a requirement for supplemental O₂ at 36 weeks’ postmenstrual age, compared with a control group recruited from the EP/ELBW subjects classroom. They describe 34 EP/ELBW subjects as having received surfactant, no further details are given. They performed a symptom-limited incremental cardiopulmonary exercise test on a cycle ergometer. They showed EP/ELBW subjects had significant reductions in peak oxygen consumption, increased breathing frequency, increased use of ventilatory reserve, with decreased tidal volumes, oxygen pulse and work rate in EP subjects compared with control subjects.

Kilbride et al. published data on 46 EP/ELBW adolescent children, aged 11.3±1.6 years (mean GA 26.1±1.6 weeks at birth; mean birth weight 701±80 grams), 16 (32%) of whom had BPD defined as supplemental O₂ requirement > 36 weeks’ postmenstrual age, compared with 25 controls (NBW, >37 weeks’ GA and birth weight >2500 g). This cohort was born in the pre-surfactant era. They performed cardiopulmonary exercise testing using a treadmill running protocol and increased the intensity of exercise in one minute steps, interestingly they reported 4 EP/ELBW subjects were “uncomfortable with running and used a Balke-type walking protocol with a speed of 3.4 miles per hour”, differing protocols may affect the final outcomes at peak exercise. Kilbride et al. state that the EP/ELBW subjects who completed the walking protocol were included in most of the analysis because “findings were not different from analysis with only the running protocol” but there were no data published to confirm this. They showed a small but statistically significant reduction in V'O₂max and O₂ pulse for the ELBW group, whether or not subjects had BPD, compared with controls.

Vrijlandt et al. report data from 42 VP/LBW young adults, aged 19±0.3 years (age range, 19-20 years; mean GA 30±2 weeks’, mean birth weight 1246±232 g), and 9 of whom had BPD defined as supplemental O₂ requirement beyond 28 days and chronic changes on chest x-ray. This cohort was born before the surfactant era. They performed a cardiopulmonary exercise test using an incremental symptom limited protocol on a bicycle ergometer. Vrijlandt et al. are the only group to reported exercise outcomes in adulthood. They showed no difference in VO₂peak with decreased ventilation rates, tidal volume, increased breathing frequency and reduced load achieved for preterm subjects compared with controls. The only difference they found when comparing those who had BPD with those who did not was a small but significant reduction in the heart rate as a percentage of predicted achieved by the No-BPD group.

Most of these studies describing cardiopulmonary exercise outcomes have small numbers of subjects, with Gross et al. and Welsh et al. the only groups with >20 subjects in each subgroup or on specifically selected patient groups, e.g. those that took part in ventilation studies or who were admitted as neonates with respiratory distress, and only Welsh et al. reported data from the
surfactant era. Smith et al. have published data on exercise outcomes in the post-surfactant era, I have not discussed their results here as they have estimated V’O₂max from other types of exercise tests where heart and respiratory rates are not measured.

In summary, of the studies report V’O₂max and maximal ventilation for preterm or low birth weight subjects approximately half show a significant reduction in preterm subjects compared with controls, and half show no difference comparing the two groups. The different results found in these studies are difficult to reconcile. These differences may be due to differences in subject characteristics among the studies, different equipment used to assess V’O₂max and ventilation, and the different exercise protocols used in each study. For example, Gross et al. reported no difference in V’O₂max and included only subjects with a mean birth weight of 1173±345 g. Whereas Kilbride et al. reported a significantly lower V’O₂max in preterm subjects, with a mean birth weight of 701±107 g compared with controls, both cohorts were from the pre-surfactant era and performed exercise testing using treadmills, although had different protocols for the exercise tests. Both studies, reporting exercise data in the post-surfactant era who a reduction in V’O₂max, there is no consistent pattern in the pre-surfactant era studies. There is also no consistent pattern associated with V’O₂max or maximal ventilation and age. There are currently only two studies reporting V’O₂max in the post-surfactant era, and one study reports estimated or calculated V’O₂max from other forms of exercise.

Some of the studies in Table Spre-date the widespread use of surfactant into clinical practice, with cohorts born before 1990, whereas other studies comprise subjects born in recent years, when surfactant therapy was freely available. Some are regional cohorts, with the intention of assessing as many survivors as possible from a defined geographical region; this reduces selection biases and hence makes any results more widely applicable. Other studies are highly selective, sharing characteristics for example having been ventilated or having had BPD in the newborn period. The applicability of the results from these studies to all preterm survivors is less clear than for complete geographical cohorts. Other characteristics of those selected for study, such as birth weight or gestational age, also vary widely.
Table 5: Selected cross-sectional exercise test data from studies of EP/ELBW birth survivors, including some with BPD.

<table>
<thead>
<tr>
<th>Authors (Cohort years of birth)</th>
<th>Age (years)</th>
<th>Participants</th>
<th>GA(weeks) BW(g)</th>
<th>Protocol</th>
<th>Results mean±SD or mean[SD]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kriemler et al. (1988-1990)</strong>&lt;sup&gt;(265)&lt;/sup&gt;</td>
<td>5.5-7.8</td>
<td>PREM BPD 17</td>
<td>27.1± 1.9 wk 970± 285 g 28.3± 1.7 wk 1108± 202 g GA not specified 3455±595 g</td>
<td>Cycle Incremental</td>
<td>No difference in V’O₂max (BPD 32.0±4.9 vs. Control 32.8±8.3 mL/min/kg; ns) ↑RR (BPD 58.0±7.2 breath.min⁻¹ vs. No BPD 43.4±10.4 breaths.min⁻¹, p&lt;0.001) ↓Vt (BPD 0.40±0.006 L vs. No BPD 0.49±0.009 L, p&lt;0.05) ↑V’O₂/P (BPD 16.5±4.0 mL.min.W⁻¹ vs. No BPD 13.6±1.8 mL.min.W⁻¹ [p&lt;0.05], vs. control 13.5±2.2 mL.min.W⁻¹ [p&lt;0.01])</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PREM No BPD 14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control 24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gross et al. (1985-1986)</strong>&lt;sup&gt;(204)&lt;/sup&gt;</td>
<td>7</td>
<td>VP VLBW BPD 43</td>
<td>27±2 wk 1053±356 g 29±2 wk 1270±306 g 40.0±1.1 wk 3565±427 g</td>
<td>Treadmill Graded</td>
<td>No difference in V’O₂max (BPD 41.1±7.5 vs. control 43.2±8.6 mL/min/kg; ns) ↓HRpeak (BPD 192±14 beats.min⁻¹ vs. control 199±10 beats.min⁻¹ [p&lt;0.005]; No BPD 193±10 beats.min⁻¹ vs. control [p&lt;0.001]) ↑EIB (BPD FEV1 &lt;80% post exercise in 54% vs. control 17%; p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VP VLBW No BPD 53</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control 108</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Santuz et al. (1981-1987)</strong>&lt;sup&gt;(255)&lt;/sup&gt;</td>
<td>8.1±1.8 years</td>
<td>PREM BPD 12</td>
<td>30±2 wk 1400±335 g 39±1 wk 3335±418 g</td>
<td>Treadmill</td>
<td>↓V’O₂max (BPD 25.2±10.3 mL.min.kg⁻¹ vs. control 37.1±10.4 mL.min.kg⁻¹; p&lt;0.01) ↓V’E (BPD 20.8±9.8 L.min⁻¹ vs. control 30.7±7.9 L.min⁻¹; p&lt;0.01) ↑EIB (BPD FEV1 post exercise -8±6% vs. control -2±1%; p&lt;0.01; only 2 subjects ↓ FEV₁ post exercise&gt;15%)</td>
</tr>
<tr>
<td></td>
<td>8.1±1.5 years</td>
<td>Control 16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pianosi et al. (1986-1987)</strong>&lt;sup&gt;(266)&lt;/sup&gt;</td>
<td>8.8 years</td>
<td>PREM BPD 17</td>
<td>All PREM 28.3 (range, 24-31) wk 1165 (range, 770-1850) g</td>
<td>Cycle Incremental</td>
<td>↓V’O₂max (40±6 mL.min.kg⁻¹ vs. control 46±8 mL.min.kg⁻¹; p&lt;0.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PREM (HMD) No BPD 15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control 15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Barker et al. (1983-1989)</strong>&lt;sup&gt;(267)&lt;/sup&gt;</td>
<td>9.8 (range, 8-14) years 10.4 (range, 8-14) years 10.5 (range, 8-12) years</td>
<td>BPD 13</td>
<td>30.3 (range, 28-33) wk 1139 (range, 710-1480) g 33.5 (range, 30-36) wk 1264 (900-1490) g GA not specified BW not specified</td>
<td>Cycle Constant Load Incremental</td>
<td>No difference in V’O₂max (BPD 35.1±9.0 mL.min.kg⁻¹ vs. No BPD 36.9±5.1 mL.min.kg⁻¹ vs. control 40.8±6.2 mL.min.kg⁻¹; ns) ↓WR (BPD 2.7±0.7 Watts.kg⁻¹ vs. No BPD 2.9±0.5 Watts.kg⁻¹ vs. control 3.5±0.4 Watts.kg⁻¹; p&lt;0.005) ↓V’E (BPD 40.5±11.5 L.min⁻¹ vs. No BPD 47.2±16.0 L.min⁻¹ vs. control 54.6±9.1 L.min⁻¹; p&lt;0.005)</td>
</tr>
<tr>
<td>Study</td>
<td>Age Range</td>
<td>Preterm Group</td>
<td>Control Group</td>
<td>Exercise Protocol</td>
<td>Findings</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-----------</td>
<td>---------------</td>
<td>---------------</td>
<td>-------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Baraldi et al. (1976-1979) (268)</td>
<td>9.9±1.8 years</td>
<td>PREM AGA 9</td>
<td>30.0 ± 1.5 wk 1302 ± 164 g 35.3 ± 1.5 wk 1263 ± 117 g 31.47±6 wk 3226±167 g</td>
<td>Treadmill</td>
<td>No difference in V'O₂max (VLBW 42.9±9.1 mL.min.kg⁻¹ vs. control 42.7±9.9 mL.min.kg⁻¹, ns; SGA 43.4±11.0 mL.min.kg⁻¹ vs. AGA 42.1±8.6 mL.min.kg⁻¹ vs. control, ns)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PREM SGA 6</td>
<td></td>
<td></td>
<td>↑Energy cost (SGA vs. control, p&lt;0.025; no values given this is represented graphically)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smith et al. (1992-1994) (269)</td>
<td>10.1±1.1 years</td>
<td>VP/ELBW 126 (BPD 37)</td>
<td>26.9±1.7 wk 862.4±160.9 g 39.4±1.2 wk 3401±513 g</td>
<td>6-minute walk Shuttle test Calculated V'O₂</td>
<td>↓Shuttle distance (PREM median 300 (range, 40-940) m vs. control median 680 (range, 280-1680) m, p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control 34</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jacob et al. (1981-1987) (270)</td>
<td>11.2±1.5 years</td>
<td>PREM BPD 15</td>
<td>28.7±2.1 wk 1110±328 g 28.5±2.6 wk 1044±263 g</td>
<td>Cycle</td>
<td>No difference in V'O₂max (BPD 36.1±7 mL.min.kg⁻¹ vs. No BPD 36.7±9.2 mL.min.kg⁻¹ vs. control 37.9±5.3 mL.min.kg⁻¹, ns)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PREM No BPD 15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control 13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Welsh et al. (1995) (271)</td>
<td>11.1±0.4 years</td>
<td>EP 38</td>
<td>median 25.0 (IQR, 24.7-25.1) wk 740±107 g median 40.0 (IQR, 40.0-40.4) wk 3360±527 g</td>
<td>Cycle Incremental</td>
<td>▾V'O₂max mean difference (EP 1293±271 mL.min⁻¹ vs. control 1590±263 mL.min⁻¹; p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Controls 38</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kilbride et al. (1983-1989) (260)</td>
<td>11.3±1.6 years</td>
<td>ELBW 50 (BPD 16)</td>
<td>26.1±1.6 wk 701±80 g &gt;37 wk &gt; 2500 g</td>
<td>Treadmill Incremental running + walking protocol</td>
<td>▾V'O₂max (BPD 1.3±0.4 L.min⁻¹ vs. control 1.65±0.44 L.min⁻¹; p&lt;0.05; No BPD 1.32±0.45 L.min⁻¹ vs. control; p&lt;0.01)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Controls 25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11.1±1.3 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vrijlandt et al. (1983) (80)</td>
<td>19±0.3 years</td>
<td>PREM 41 (BPD 8)</td>
<td>30±2 wk 1246±232 g 37-42 wk BW not specified</td>
<td>Cycle Incremental</td>
<td>No difference in V'O2max (PREM 35.3±6.9 mL.min.kg⁻¹ vs. control 37.4±6.3 mL.min.kg⁻¹; p=0.1) ↓V'E (PREM 70.0±17.9 L.min⁻¹ vs. control 80.9±20.8 L.min⁻¹, p=0.01) ↓Vt (PREM 0.53±0.12 L vs. control 0.63±0.26 L, p=0.03) ↑BF (PREM 16±3 breaths.min⁻¹ vs. control 14±3 breaths.min⁻¹, p&lt;0.001) ↓Load (PREM 185.4±36.9 Watts vs. control 218.4±41.2 Watts; p&lt;0.001) ↓HR (BPD 92.3±4.4 %pred vs. No BPD 86.8±6.0 %pred, p=0.04)</td>
</tr>
<tr>
<td>20.8±1.2 years</td>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values expressed as mean (SD) unless otherwise stated; V'O2 – oxygen consumption; V'O2peak: oxygen consumption at peak exercise; V'E – ventilation rate at peak exercise; MVV – maximum voluntary ventilation; RR – respiratory rate; HRpeak – heart rate at peak exercise; Wmax – load (watts) at peak exercise; Vt – tidal volume; SpO2 - oxygen saturation; BF – Breathing frequency (breaths/min); O2Pulse - Oxygen pulse (mLs/beat); VO2/P – an index of the O2 cost at a given mechanical power;
5.1.6.1.4 Respiratory Morphology

There is a paucity of information regarding lung structural abnormalities in preterm or LBW survivors. Aukland et al. published a study analysing the results from pulmonary high-resolution computed tomography (HRCT) scanning and pulmonary function tests in a group of 74 EP/ELBW subjects. They reported lung parenchymal abnormalities in 64 subjects (86%) and demonstrated a negative correlation between FEV₁ and the extent of HRCT abnormalities. Wong et al. reported similar results in a group of VP/VLBW subjects with a median age 19 years (range, 17-33 years) and showed all 19 subjects had abnormal findings on HRCT, with the most common abnormality being emphysema (84% of subjects). Wong and colleagues also found the emphysema correlated with abnormal pulmonary function, including reduced expiratory flow rates, gas trapping and DLCO. Ideally, I would have liked to perform HRCT on the subjects in the current study to assess lung structure, unfortunately time and cost constraints meant was unable to.

5.1.7 Summary

Over the past 40 years there have been important advances in neonatal care that have dramatically improved survival of the most immature infants. Despite this BPD remains a major cause of respiratory morbidity and mortality among preterm babies. There is no single approach or treatment that has been shown to prevent or treat BPD. Due to their prematurity, the lungs of EP infants are more immature and have less surface area for gas exchange, a thicker blood-gas barrier, and fewer type II epithelial cells (to produce surfactant) compared with their term born peers. The structural immaturity of the acinar air spaces alongside surfactant deficiency means more immature lungs may not be as efficient at gas exchange. This immaturity of development in which the lungs fail to reach their full structural complexity and a reduced surface area for gas exchange have been suggested as causes for BPD. The rates of BPD, the most common chronic respiratory condition affecting preterm infants, increased alongside the improved survival of these smaller, less mature infants. The newer BPD is defined as the need for supplemental oxygen for at least 28 days after birth, and its severity is graded according to the level of respiratory support required at 36 weeks’ post-menstrual age for infants born less than 32 weeks’. There have been very few randomised controlled studies that have looked at specific interventions to treat BPD, apart from postnatal corticosteroids. This is in part because lung function impairments in children with BPD improve with time due to the normal repair processes within the lungs. It is difficult to distinguish lung function improvements from the treatment effects or from improvements that occur as part of the normal repair process.
Advances in perinatal and neonatal care over the past few decades have produced notable achievements in reducing neonatal mortality and morbidity due to complications of pregnancy, labour, delivery and the consequences of preterm birth. Oxygen therapy, mechanical ventilation, invasive physiologic monitoring and surfactant therapy are important examples. Yet despite these achievements, in some areas, especially prematurity, outcomes have remained similar for the past 15 years. The National Institute of Child Health and Human Development reported that between 1994 and 2000 in VLBW infants that mortality from diseases such as IVH, NEC and BPD had not changed significantly, and BPD remained the lead respiratory morbidity. The main risk factor for BPD is preterm birth, but prevention of preterm birth is not likely to occur in the near future as there is still a lack of understanding of the pathophysiology behind preterm labour.(96) Preterm birth research suggests that respiratory symptoms are present from infancy to childhood and while these symptoms decrease with time, evidence suggests these respiratory symptoms can remain in adult preterm survivors. In terms of pulmonary function, abnormal lung function persists, especially variables related to airflow, diffusion capacity, and air trapping or hyperinflation. These patterns are also seen amongst later preterm subjects in comparison with control subjects.(273) Cardiopulmonary exercise capacity has also been shown to be abnormal in preterm survivors through to adulthood. Whether this relates to reduced DLco measured at rest, as a functional assessment of the volume and surface area available for gas exchange, that may be influenced by antenatal events or lung injury that is secondary abnormalities in the pulmonary circulation or structural abnormalities within the lungs is yet to be determined.
6 Thesis objectives

6.1.1 First objective
The primary objective of this project is to compare respiratory function and exercise capacity at 18 years of age in survivors born EP or ELBW with a control group who are born at term or who were of normal birth weight.

6.1.2 Second objective
To compare respiratory function and exercise capacity at 18 years of age in the EP/ELBW survivors who had BPD in the newborn period with EP/ELBW survivors who did not have BPD.

6.1.3 Third objective
To determine the relationships between growth restriction in utero and respiratory function and exercise capacity at 18 years of age in EP survivors.

6.1.4 Hypotheses
EP birth or ELBW will lead to airflow limitation, ventilation inefficiency, reduced transfer factor of the lung and impaired exercise capacity, compared with controls.

EP/ELBW subjects with BPD will have more lung function and exercise abnormalities than those EP/ELBW subjects who did not have BPD.

Growth restriction in utero amongst the EP only subjects will lead to further impairment of lung function and exercise capacity.
7 Methods

7.1 Study design

This study is a prospective longitudinal regional cohort study from the state of Victoria of all survivors either <28 weeks’ gestational age or <1000 g at birth born in either 1991 or 1992.

7.2 Recruitment

The group has been followed-up on previous occasions and contact details kept as current as possible. The recruitment method for this stage of the longitudinal study involved sending out an initial information package, including a project outline, or contacting the family by telephone all of which was completed by Research Nurse Coordinators from the Victorian Infant Collaborative Study (VICS) Group. Appointments were made for each participant to attend the Respiratory Department at the Royal Children’s Hospital at a mutually agreeable time by the VICS coordinators and me. Participants were encouraged to discuss this with family and friends or a medical practitioner, and to contact researchers if they had any queries or concerns. All participants, if capable, or their parents or guardians gave written informed consent to participate in the study, which was approved by the Human Research Ethics Committees of the Royal Women’s Hospital and the Royal Children’s Hospital (HREC #28034). I constructed the testing protocol for the lung function and exercise components of this study, which was used in the Ethics application. All lung function and cardiopulmonary exercise testing was conducted by me. I was assisted during cardiopulmonary exercise testing by clinical staff as a safety precaution.

7.3 Participants

The VICS Group was created to determine population-based data for children born at extremely low gestations or extremely low birth weights. The EP/ELBW cohort originally comprised 298 consecutive live births with either birth weight <1,000 g or gestational age <28 weeks, born in the state of Victoria, Australia, during 1991–1992. The control group comprised 262 randomly selected normal birth weight, (birth weight, >2,499 g) survivors, most of whom were also term (>36 weeks’ gestational age). Controls were matched with the EP/ELBW cohort on gender, mother’s health insurance status, and country of birth, and were randomly selected from those eligible born on the date that an EP/ELBW survivor was expected to be born. Exogenous surfactant was introduced into clinical care in Victoria in March 1991.

BPD was defined in the EP/ELBW groups as clinical signs of respiratory distress with an oxygen requirement at 36 weeks of postmenstrual age. The NICHD definition of BPD, including defined severity levels, has not been applied for this study as they were recruited in 1991-1992 before this definition had been published and cannot be applied retrospectively as the FiO₂ data was not collected; only data relating to oxygen days was collected.
Data on the outcomes of these cohorts at 2(274,275), 5(140), and 8(276) years of age have been reported, including lung function at 8 years of age.(186) The cohorts were reassessed in late adolescence, at approximately 18 years of age. The respiratory function and cardiopulmonary exercise testing is one component of this follow-up at 18 years of age. The study also included other components assessing the physical (respiratory, cardiovascular, growth, neurological), cognitive (IQ, processing speed, attention, memory, visual-spatial processes, executive function), educational (basic academic skills, school progress), social-emotional, (social skills, self-esteem, quality of life), and mental health (attention deficit-hyperactivity disorder (ADHD), depression, anxiety, substance use) problems experienced by these preterm subjects in adolescence compared with normal birth weight controls.

7.4 Tests

7.4.1 Static Lung Function

Testing lasted approximately 90 minutes in total. Lung function testing was performed in the Department of Respiratory Medicine at the Royal Children’s Hospital Melbourne. Spirometry was performed on the Jaeger Bodyplethysmograph (Jaeger MasterScreen body, Würzburg, Germany) and Labmanager V4.67a software. The spirometer was calibrated daily for volume using a 3L + 0.4% syringe (Viasys Healthcare, Würzburg, Germany, serial number 95318048, calibration valid July 2009). Participants were seated in the plethysmograph and wore a nose clip when they performed the lung function manoeuvres. Firstly, the operator explained the spirometry test and demonstrated the appropriate technique. Participants were then instructed to place their teeth and lips around the disposable bacterial/viral filter (Suregard, BIRD Healthcare, Victoria, Australia), and following one or two preliminary breaths, to inhale as deeply as possible and then to exhale maximally until no more air could be expelled, while maintaining an upright posture. Forced expiratory testing was conducted, with the door of the plethysmograph open to obtain values for FEV$_1$, FVC and forced expiratory flows. Testing was carried out according to American Thoracic Society and European Respiratory Society criteria. The testing was repeated six to eight times until at least two readings of FEV$_1$ were achieved that agreed to within 150 ml.(28,277)

Plethysmography was performed to measure TLC, FRC (TGV), RV, $sR_{tot}$ and $sR_{eff}$. These measurements were obtained using a body plethysmograph (Jaeger MasterScreen body, Würzburg, Germany) with electronic body temperature and pressure saturated water vapour compensation at a constant volume of 850 L. Body plethysmography measures the total gas in the thoracic cage (and the small amount in the abdominal and oral cavities), irrespective of whether the gas is freely communicating or trapped behind obstructed airways. The gas dilution techniques can measure only that gas which is freely communicating. The total lung capacity (TLC)
refers to the volume of air in the lungs after a full inspiration or breath in, or the sum of all the sub-divisions. The vital capacity is the total volume from either full inspiration to full expiration or full expiration to full inspiration. The pressure transducer for internal box pressure is automatically calibrated and the box time constant or half-life is measured with this calibration. The half-life value allows detection of leakage from the box. The box was calibrated daily, following the volume calibration described in the spirometry section above, according to relevant guidelines. Participants were seated in the plethysmograph, with the door firmly shut, wore a nose clip and supported their cheeks with the palms of their hands. Participants were instructed to place their teeth and lips around the disposable bacteria/viral filter (Suregard® BIRD Healthcare, Victoria, Australia), and asked to breathe at a rate of 35 to 45 breaths per minute for up to one minute. When a stable tidal breathing (Vt) baseline is established the mouthpiece is occluded at end expiration respiratory efforts are measured against the occlusion for 2 seconds. The pressure, flow and volume changes that occur at this point are representative of the gas remaining in the lungs at the end of a normal tidal breath; this is known as the thoracic gas volume (TGV). The participant resumes tidal breathing and was then asked to inspire fully to Total Lung Capacity (TLC), the inspired volume from Tidal Volumes to TLC is the Inspiratory Reserve Volume (IRV), then expire fully to reach Residual Volume (RV). These capacities and volumes are known as sub-divisions of Total Lung Capacity or Lung Volume.

Specific airways resistances ($sR_{tot}$ and $sR_{eff}$) were measured during tidal breathing (Master Screen Body Plethysmograph, version 5; CareFusion; Hochberg, Germany). Subjects sat alone in the plethysmograph wearing a nose clip. They were asked to breathe quietly at a rate of 30 to 45 breaths per min through the mouthpiece; three trials of 10 loops were recorded. According to recent guidelines, results of both specific airways resistance ($sR_{aw}$), calculated by integration of multiple pressure/flow points throughout the breathing cycle, and total specific resistance ($sR_{tot}$), calculated between points of maximum pressure change, are presented as median values from the most representative (i.e., median) trial. For each $\Delta V_{box}/\Delta V_{mouth}$ loop appearing on the computer monitor (Figure 11).

Results at body temperature and pressure saturated with water vapour were expressed as a z-score for age, height and gender according to reference data from Stanojevic and colleagues. Ratios (RV/TLC) were expressed as % values.

$DL_{CO}$ was measured by the single breath method in the Jaeger bodyscreen diffusing capacity device. Gas analyser calibration was performed daily to calibrate the built in gas analyser for Carbon monoxide (CO) and Helium (He) which determines the gas values in the measurement program $DL_{CO}$. During inspiration, the patient inhales a premixed gas consisting of He, CO and air directly from a gas cylinder controlled by a demand valve.

The gas cylinder has the following concentrations:
CO = 0.20 – 0.30 %  
He = 7.0 – 10.0 %  

Remainder is synthetic air; Oxygen and Nitrogen. Before starting a measurement, both gas analysers (CO and He) are zeroed using ambient air. Volume calibrations were carried out as described in the spirometry section above. A volume of 90% vital capacity as measured in spirometry was used for breath holding for all children. (216,279) Both washout volume and sample volume were pre-set at 600 mL. Two to four tests were performed at intervals of 4 minutes. (216,279) The subjects had pathology samples collected by venepuncture and haemoglobin was measured. Most subjects had 4% amethocaine gel (AnGEL) or 5% lidocaine and prilocaine in a 1:1 emulsion (EMLA) anaesthetic cream applied to their skin at least 45 minutes prior to the procedure, in adherence with Hospital policy (http://www.rch.org.au/kidsinfo/fact_sheets/Reduce_childrens_discomfort_during_tests_and_procedures/). DLco was corrected for haemoglobin, calculated according to Cotes. (216,279) Results were considered acceptable if they met the acceptability criteria defined by the ATS/ERS standardisation of lung function testing document. (46) Briefly, the inspired volume had to be at least 85% of the vital capacity, as measured by spirometry, and take less than 4 seconds. (46) The subsequent breath hold had to be maintained for 10±2 seconds, with no evidence of leaks, or Valsalva or Meuller manoeuvres. (46) This was followed by an expiration (<4 seconds) where there was adequate clearance of the airway dead space and adequate volume for expiratory gas sampling and analysis. (46) Mean values of acceptable measurements were used for analysis. (46,279) Results at body temperature and pressure saturated with water vapour were expressed as a z-score for age, height and gender according to reference data from Kim and colleagues. (280)

Z-scores are advantageous in longitudinal analysis as they allow standardisation of values from different populations, which can then be directly compared. The z normal distribution so derived is itself assumed to have a normal distribution. Z-scores are calculated from variables measured in a population. An example of this is height measured in a population or math test results in a school. These measurements will result in data; these data will have a distribution, which will have a mean and standard deviation (SD). In order to compare data from different populations it needs to be standardised. Transforming the data to z-scores is a form of standardisation, where the mean is transformed to zero and the SD is transformed to 1. A z-score is the number of SDs a raw score (or individual’s result) deviates from the mean and is calculated by subtracting the mean of the distribution and dividing by the SD. The sign of the z-score indicates the direction of the score, whether the individuals result falls above (positive) or below (negative) the mean. Using one of the examples above, math test results, if Child A achieves 26 points, the mean at their School is 22 with a SD of 2 points is compared with Child B who achieves
900 points, the mean at their School is 1000 with a SD of 100 points it is difficult to make a comparison. However, after standardising the results:

\[
\text{Equation 2: Child A z-score} \\
\frac{z - \text{score}}{\sigma} = \frac{26 - 22}{2} = +2
\]

\[
\text{Equation 3: Child B z-score} \\
\frac{z - \text{score}}{\sigma} = \frac{900 - 1000}{100} = -1
\]

From these findings Child A’s result is 2 SDs above the mean and Child B’s result is 1 SD below the mean. Therefore Child A’s result is relatively better. For any normally distributed variable, 50% of the scores fall above the mean and 50% fall below; approximately 68% of the scores fall within plus and minus 1 z-score from the mean; approximately 95% of the scores fall within plus and minus 2 z-scores from the mean; approximately 99.7% of the scores fall within plus and minus 3 Z-scores from the mean.

### 7.4.2 Multiple breath nitrogen washout

The multiple breath nitrogen washout (MBW) test was performed using a closed circuit “bag-in-box breathing system” to deliver 100% oxygen during inspiration with separate capture of the exhaled breath.\(^{136,224}\) The O\(_2\) source was a large gas-impermeable bag filled with dry 100% O\(_2\). The nitrogen concentration was measured at the mouth with a fast-responding nitrogen analyser, while flow and volume were recorded from a pneumotachograph flow meter connected to a one-way Hans Rudolph Inc. valve to allow for the separate capture of exhaled breath to and prevent rebreathing. The nitrogen analyser had been previously calibrated against a set of nine Oxygen/Nitrogen National Association of Testing Authorities (NATA) approved calibration gases (ranging between 5.1 and 84.7% Nitrogen) and 100% Oxygen (0% Nitrogen).\(^{281}\) Tidal volumes were measured by volume displacement from within the bag in the box system by use of a pre-calibrated pneumotachograph (Fleish type, flow range 0–5 l/s).\(^{281}\) The participants breathed 100% O\(_2\) while maintaining a tidal volume of approximately 1 Litre until the expired nitrogen concentration fell below 2\% (1/40\text{th}) of the initial nitrogen concentration.\(^{136,224}\)

Ventilation heterogeneity indices in the conductive (Scond) and acinar (Sacin) airways were derived using an analysis algorithm to automatically determine the alveolar slope in a manner equivalent to that determined manually by the method of Verbanck et al.\(^{55,281}\) The upper limit of normal for Scond was 0.037/L, and for Sacin was 0.130/L derived from the mean + 1.96 x SD of the values obtained previously in normal subjects.\(^{136,282}\) The lung clearance index (LCI) was calculated by dividing the cumulative expired volume (CEV) during the washout by the patient’s functional residual capacity (FRC) determined from the washout.\(^{136,282}\) Three tests were performed. As a quality control measure, tests where the measured FRC differed by more than 10\% from both of the other two repeats were excluded.\(^{38}\)
The conducting airways contribution to ventilation inhomogeneity (Scond) and acinar airways contribution to ventilation inhomogeneity (Sacin) were estimated by calculating phase 3 slopes, as previously described.\(^{(136,282)}\) The mean LCI, Scond, Sacin, and FRC from three technically acceptable washouts are reported and were performed before spirometry.

### 7.4.3 Cardiopulmonary exercise

Aerobic fitness was assessed via a symptom-limited individualised progressive incremental peak exercise test on a treadmill (Jaeger, Wurzburg, Germany) with Labmanager V4.67a software. The exercise test was performed after bronchodilation with 400 mcg salbutamol inhaled via a volumetric spacer device. The protocol for the exercise test started with walking, they had increasing workload or exercise intensity so that the subject would run with encouragement to the point of exhaustion. The increase in workload was individualised for each child, as previously described.\(^{(59,283)}\) Individualisation was based on the predicted \(V'\text{O}_2\text{max}\) of each child, converted into maximum watts (Wmax), to make it easier to increase the load (in watts) during the test, the calculations for which are as follows.

**Equation 4:**

\[
\text{Baseline } V'\text{O}_2 = (\text{height in centimetres } \times 2) - 100
\]

Predicted \(V'\text{O}_2\text{max}\) was calculated according to the Wasserman normal values as a function of gender, weight, and the age of the child.\(^{(58,59)}\) The difference between \(V'\text{O}_2\text{max}\) and baseline \(V'\text{O}_2\) was calculated. Wmax corresponding to this difference was calculated as follows:

**Equation 5:**

\[
W_{\text{max}} = \frac{(\text{predicted } V'\text{O}_2\text{max} - \text{baseline } V'\text{O}_2)}{10.3}, \text{ where } 10.3 \text{ mL of } O_2/\text{min/W is the equivalent in oxygen of each watt.}\(^{(58)}\)
\]

The Wmax was then divided by 8 to define the workload increase for each 1-minute stage of the exercise test, in order for the test to last between 8 and 10 minutes, see Appendix 1 for an example. Maximum voluntary ventilation was estimated as 35x FEV\(_1\). Expired gases were analysed using a Jaeger CPX system to obtain the oxygen uptake and carbon dioxide production. Subjects were verbally encouraged to give a maximal effort.\(^{(284)}\) A participant’s effort was considered maximal if the peak heart rate (HR) was > 90% predicted (predicted HR = 220-age), the respiratory exchange ratio (RER) was >1.05 and a maximal effort were deemed to have been exerted. Throughout the exercise test subjects breathed through a mouthpiece attached to a turbine flow meter and gas analysers. When air moves through the turbine it forces a vane within the flow meter to move the tube, which is proportional to the number of revolutions per unit of time. Flow is then determined by the number of electrical impulses generated by the vane interrupting light from a light source on one side of the flow meter to the photocell located on the opposite side with each turn of the vane. During tidal breathing subjects wore a nose clip and all
air passed through the flow meter, oxygen analyser and carbon dioxide analyser allowing for breath-by-breath analysis. The following variables were measured: minute ventilation (V'E), oxygen uptake (V'O₂), carbon dioxide production (V'CO₂) and respiratory exchange ratio (RER). Heart rate was monitored continuously by 12-lead electrocardiography (Jaeger, Wurzburg, Germany). The variables such as oxygen uptake and workload measured in the last 30 seconds of exercise prior to completion of the test were considered peak values. Throughout the exercise and recovery periods, continuous ECG and oxygen saturation monitoring was carried out.

Stroke volume in this instance is calculated using an adaptation of Fick’s equation where:

**Equation 6:**

\[
\text{Cardiac output} = \text{Heart rate} \times \text{stroke volume}
\]

Rearranging:

\[
\text{Stroke volume} = \frac{\text{Cardiac output}}{\text{HR}}
\]

Substituting:

\[
\begin{align*}
\text{Stroke volume at the anaerobic threshold (AT)} &= \text{oxygen pulse at the AT} \times \\
&\frac{150}{\text{haemoglobin}} \times 10
\end{align*}
\]

\[
\begin{align*}
\text{Stroke volume at the maximal exercise} &= \text{oxygen pulse at the maximal exercise} \times \\
&\frac{150}{\text{haemoglobin}} \times 10
\end{align*}
\]

This calculation assumes SpO₂ is stable during exercise and at maximal exercise the arterio-venous difference is 0.65 (= CₐO₂ - CᵥO₂ = 0.9 – 0.35).(285)

Results were compared with controls as no relevant predicted values are available at present.(286) The selection of reference values for comparison of results is imperative to interpreting the results from cardiopulmonary exercise tests. Reference values and normal ranges provide the basis for deciding whether results are normal, and if they are abnormal how abnormal they are and what treatment strategies should be implemented. When selecting reference values it is important to consider the sample size of the study, quality assurance of the exercise mode and protocols, data validation, and statistical interpretation of the data set.

### 7.4.4 Outcome variables

#### 7.4.4.1 Spirometry

The outcome variables, which are forced expiratory volume in 1 second (FEV₁), forced vital capacity (FVC), forced expiratory flow between 25% and 75% of the FVC (FEF₂₅₋₇₅) and the ratio of FEV₁/FVC, are all continuous. The original measurements were recorded at body temperature and pressures saturated with water vapour (BTPS), and were standardised for age, height and gender for analysis, by converting the raw data to z-scores according to reference data from Stanojevic and colleagues.(36) The Stanojevic data cover all of the ages that are involved in this study. Bronchodilator response (BDR) is also included as an outcome variable; this was calculated as a percentage change in FEV₁ measured pre and post 400 mcg Salbutamol, administered by a
metered dose inhaler and volumetric spacer device. A change in BDR values >12% compared with baseline were considered significant bronchodilation.(33)

7.4.4.2 Lung volumes

The outcome variables, including total lung capacity (TLC), functional residual capacity as measured by intra-thoracic gas volume (FRCpleth), residual volume (RV) and the ratio of RV to TLC (RV/TLC%) are continuous. There is no published reference data that cover the entire age range tested in the study. Therefore, the most appropriate reference data for those aged 15-18 years and 18+ years respectively were used. It is noted that the reference data for these two age ranges were obtained from 2 different populations. This was adjusted for in the analysis by including reference set as an interaction term in the model. All variables except airway resistance were measured in BTPS and were standardised for age, height and gender for analysis by converting the raw data to z-scores according to reference data from Zapletal (5-18 years) and Quanjer (18+ years), as recommended by Stocks and colleagues.(36). The airway resistance measures, specific airways resistance (sRtot; kPa.s⁻¹), and specific effective airways resistance (sReff; kPa.s⁻¹), do not have any age-appropriate reference equations therefore the multivariable linear regression models are adjusted for the explanatory variables age, height and gender where they were significantly associated (p-value < 0.05). The results are reported as the regression coefficient for the group and 95% confidence intervals (CIs), as there are no appropriate reference data for the age range in this study.

7.4.4.3 Transfer factor

The outcome variables, Transfer factor or Diffusion capacity of the Lung for Carbon monoxide (DLco), alveolar volume VA and the ratio of DLco/VA (DLco/VA%), are all continuous. No published reference data exist that cover the age range of this study. Therefore, the most appropriate reference data for those aged 15-19 years and 19+ years respectively were used. The fact that 2 different reference populations are being used for standardisation mean that the reference set was adjusted for in the analysis. The raw data were recorded in BTPS and were standardised for age, height and gender for analysis by converting the raw data to z-scores according to reference data from Kim (5-19 years) and ATS (19+ years) as recommended by Stocks and colleagues.(36)

7.4.4.4 Multiple breath nitrogen washout

The variables, including Lung Clearance Index (LCI), ventilation heterogeneity in the conducting airways (Scond) and ventilation heterogeneity in the acinar airways (Sacin) are continuous. The raw data for LCI was standardised for age, height and gender for analysis by converting the raw data to z-scores according to reference data from Kim (5-19 years) and ATS (19+ years) as recommended by Stocks and colleagues.(36)
data to z-scores according to reference data from Lum et al. (50) Ideally, I would like to have a local control population who completed testing on similar equipment to use to create reference data for these indices. The reference equations from Lum et al represent the closest estimate of the population in the study and converting the MBW data to z-scores allows direct comparison with the other lung function results. (50) The age range for those who completed LCI successfully was 16.4 to 19.3 years of age. There is no published reference data for Sacin or Scond that cover the entire age range tested in the study, hence raw measurements were used for analysis.

### 7.4.4.5 Cardiopulmonary exercise

The cardiopulmonary exercise variables are all continuous. There is no published reference data that cover the entire age range tested in the study. Therefore, raw values were used for analysis; multivariable linear regression models were adjusted for the explanatory variables age, height and gender. The results were reported as the regression coefficient for the group and 95% confidence intervals (CIs), as there are no appropriate reference data for the age range in this study. The following continuous variables were contrasted between groups:

- **metabolic indices**
  - maximal work rate (Workmax; W)
  - maximal oxygen consumption per given work rate ($V'O_2/Work; mL.min.W^{-1}$)

- **cardiovascular function indices**
  - maximal heart rate (HRmax; beats.min$^{-1}$)
  - oxygen pulse, oxygen delivered per heart beat ($O_2$pulse; mL.beat$^{-1}$)
  - stroke volume at the anaerobic threshold (SV at AT; mL)
  - haemoglobin (g.L$^{-1}$)

- **ventilatory function indices**
  - maximal ventilation ($V'Emax; L.min^{-1}$)
  - maximal breathing frequency or maximal respiratory rate (BFmax; breaths.min$^{-3}$)
  - maximal tidal volume (Vtmax; L)
  - maximal inspiratory duty cycle (Ti/Ttot)
  - ventilatory reserve or respiratory reserve ($V'E/MVV, \%$)

- **gas exchange indices**
  - maximal oxygen consumption ($V'O_2max; mL.min^{-1}$ and mL.min.kg$^{-1}$)
  - maximal oxygen saturation (SpO$_2$max; \%)
  - maximal carbon dioxide production ($V'CO_2max; mL.min^{-1}$)
  - ventilatory equivalent for oxygen ($V'E/V'O_2$)
ventilatory equivalent for carbon dioxide (VE/\text{V'}CO_2)

fractional expired carbon dioxide (FETCO_2; kPa)

metabolic acidosis indices

o oxygen consumption at the ventilatory or anaerobic threshold (VO_2 at AT; ml.min^{-1})

7.4.5 Analysis Methods

Prior to starting testing participants, I received advice from the Clinical Epidemiology and Biostatistics Unit and the Murdoch Children's Research Institute and Royal Children's Hospital, Melbourne (CEBU; http://www.mcri.edu.au/research/core-facilities/cebu/) who advised me on the analysis methods and how to present the outcome measure in the most appropriate way for the study. All of the subsequent analysis I have conducted on my own. Z-scores were calculated from the available reference data for the following outcome variables: FEV₁, FVC, FEF_{25-75}, FEVR, TLC, FRC_{pleth}, RV, FRC/TLC%, RV/TLC%, DL_{CO}, V_A and DL_{CO}/VA%. The reference equations used to calculate TLC and RV from Zapletal et al. (5-18 years; coded as 1 in the model) and Quanjer et al. (18+ years; coded as 0 in the model) are recommended by the American Thoracic Society and European Respiratory Society, there are 2 different sets used one for those ≤ 18 years and a second set for those > 18 years of age. (287) The reference equations used to calculate V_a are from Kim et al. (≤ 19 years; coded as 1 in the model) and American Thoracic Society (> 19 years; coded as 0 in the model). (47,63) These z-scores were summarised as the regression coefficient for the group and 95% confidence intervals (CIs).

Where no appropriate published data exist, raw values were used in the analysis. This applied to the following outcome variables: sR_{tot}, sR_{eff}, peakvo2, peakhr, peakspo2, peakbf, peakfetco2, peakpetco2, peakrer, peakvtex and peakttot. Multivariable linear regression models for these variables were adjusted for the explanatory variables age, height and gender where they were significantly associated (p-value < 0.05). The results were reported as the regression coefficient for the group and 95% confidence intervals (CIs), as there are no appropriate reference data for the age range in this study.

The following index variables were also reported: LCI, sCond and sAcin, and summarised as the regression coefficient for the group and 95% confidence intervals (CIs).

Descriptive statistics, such as mean (SD) and regression analysis were used to compare lung function and exercise capacity variables between the groups list below. These and subsequent analysis were performed using STATA (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

The outcome variables listed above were compared between the following groups:
• NBW vs. EP/ELBW (objective 1)
• BPD vs. No BPD (EP/ELBW survivors only, objective 2)
• EP regressed against birth weight z-score (EP survivors only)

Groups were compared by unadjusted linear regression where standardisation was possible from a single source, e.g. spirometry. For outcomes where the results were standardised but using more than one set of reference data, e.g. TLC, RV and DLCO, again linear regression was used to compare groups, although in these analyses the models included a variable for the population that the participant was standardised using, generally <18 vs. 18+ years of age (for DLCO < 19 vs. 19+ years of age) as an explanatory variable. For outcomes where no standardisation was possible, e.g. airway resistance and cardiopulmonary exercise outcome variables, multivariable linear regression models were adjusted for the explanatory variables age, height and gender. The results were reported as the regression coefficient for the group and 95% confidence intervals (CIs).
8 Results

8.1 Respiratory function and exercise capacity at 18 years of age in EP/ELBW survivors versus the control group.

8.1.1 Population characteristics

Of the eligible 298 EP/ELBW survivors, 208 (70%) had lung function data at the 18 year follow-up. Table 6 compares perinatal data of those within the EP/ELBW groups who attended and were tested and those who did not attend and therefore were not tested at the 18-year follow-up. Within the EP/ELBW group, perinatal data in those tested and not tested at this follow-up was similar.

Table 6: Perinatal data comparing the EP/ELBW who were tested at the 18-year follow-up and those who were not.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lung function at 18 year follow-up</th>
<th>Significance test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes=208 (69.8%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No=90 (30.2%)</td>
<td></td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>94 (45%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>45 (50%)</td>
<td></td>
</tr>
<tr>
<td>Birth weight (BW), g</td>
<td>889 (162)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>884 (161)</td>
<td></td>
</tr>
<tr>
<td>zBW</td>
<td>-0.43 (1.41)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-0.59 (1.54)</td>
<td></td>
</tr>
<tr>
<td>GA, completed weeks</td>
<td>26.7 (2.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>26.8 (1.7)</td>
<td></td>
</tr>
<tr>
<td>BPD, n (%)</td>
<td>73 (35%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>38 (42%)</td>
<td></td>
</tr>
<tr>
<td>IPPV, median days (IQR)</td>
<td>17 (5-31)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20 (5-33)</td>
<td></td>
</tr>
<tr>
<td>Oxygen therapy, median days (IQR)</td>
<td>48 (16-86)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>59 (24-94)</td>
<td></td>
</tr>
<tr>
<td>Antenatal corticosteroids, n (%)</td>
<td>148 (70.8%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>69 (77.5%)</td>
<td></td>
</tr>
<tr>
<td>Postnatal corticosteroids, n (%)</td>
<td>64 (30.6%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>34 (38.2%)</td>
<td></td>
</tr>
<tr>
<td>Level III care, median days (IQR)</td>
<td>78 (58-100)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>82 (63-100)</td>
<td></td>
</tr>
<tr>
<td>Surfactant, n (%)</td>
<td>83 (39.7%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>36 (40.5%)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity, n European descent (%)</td>
<td>180 (86.1%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>70 (78.7%)</td>
<td></td>
</tr>
<tr>
<td>Mode of delivery, n Caesarean (%)</td>
<td>76 (35.5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>38 (42.2%)</td>
<td></td>
</tr>
<tr>
<td>Multiple birth, n (%)</td>
<td>69 (30.5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>22 (24.7%)</td>
<td></td>
</tr>
</tbody>
</table>

Variables are expressed as mean (SD), unless otherwise stated; Significance test difference in proportions by $\chi^2$ analysis unless otherwise stated; IQR=Interquartile range †Difference in medians by Wilcoxon-Mann-Whitney test; §Difference in means by t-test

Of the 261 eligible controls, 153 (59%) had lung function data at the 18-year follow-up. Within the control group, perinatal data in those tested and not tested at this follow-up were mostly similar (Table 7). However, the proportion of males tested was less than the proportion not tested, and the proportion of control subjects tested who were born as part of a multiple pregnancy was less than in the group of control subjects not tested.
Table 7: Perinatal data comparing the control group who were tested at the 18-year follow-up and those who were not.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lung function at 18 year follow-up</th>
<th>Significance test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes= 153 (58.8%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No= 108 (41.2%)</td>
<td></td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>64 (41.6%)</td>
<td></td>
</tr>
<tr>
<td>Birth weight (BW), g</td>
<td>3409 (465)</td>
<td></td>
</tr>
<tr>
<td>zBW</td>
<td>0.25 (0.93)</td>
<td></td>
</tr>
<tr>
<td>GA, completed weeks</td>
<td>39.2 (1.47)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity, n European descent (%)</td>
<td>137 (89.0%)</td>
<td></td>
</tr>
<tr>
<td>Mode of delivery, n Caesarean (%)</td>
<td>20 (13.0%)</td>
<td></td>
</tr>
<tr>
<td>Multiple birth, n (%)</td>
<td>2 (1.3%)</td>
<td></td>
</tr>
</tbody>
</table>

Variables are expressed as mean (SD), unless otherwise stated; Significance test difference in proportions by \( \chi^2 \) analysis unless otherwise stated; IQR=Interquartile range; \*Difference in means by t-test

Table 8 shows demographic data contrasted between the EP/ELBW and control groups followed up at 18 years. There were no differences in sex distribution or age at the 18 year follow-up between EP/ELBW and controls. As expected, there were marked differences in birth weight and GA at birth, as well as other perinatal variables between groups. The EP/ELBW were significantly lighter at birth for their gestational age, as shown by the significant different in birth weight z-score. Of the EP/ELBW group, 19% (40/208) were small for gestational age at birth (SGA; birth weight, < -1.96 SD), whereas no controls were SGA. Distribution of test age for both groups centred on approximately 18 years of age (range, 16.2 to 20.1 years). The EP/ELBW group was shorter, and lighter at time of test when height and weight z-scored, adjusted for age and gender, where compared with controls. There were no significant differences in the proportions of EP/ELBW subjects who reported asthma or current smoking compared with controls. Cigarette smoking status was derived by questionnaire, not cotinine measurement, see Appendix 2.

Table 8: Demographic characteristics of the birth weight groups at the 18 year follow-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>EP/ELBW</th>
<th>Controls</th>
<th>Mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males, n (%)</td>
<td>94 (45%)</td>
<td>64 (42%)</td>
<td>( \chi^2 (1) = 0.358; p=0.55 )</td>
</tr>
<tr>
<td>Birth weight (BW), g</td>
<td>887.6 (160.2)</td>
<td>3409.0 (464.8)</td>
<td>- |</td>
</tr>
<tr>
<td>zBirth weight</td>
<td>-0.37 (1.30)</td>
<td>0.25 (0.93)</td>
<td>-0.62 (-0.86, -0.38); p&lt;0.0001</td>
</tr>
<tr>
<td>GA, completed weeks</td>
<td>26.7 (2.0)</td>
<td>39.2 (1.5)</td>
<td>- |</td>
</tr>
<tr>
<td>BPD, n (%)</td>
<td>73 (35%)</td>
<td>0 (0%)</td>
<td>- |</td>
</tr>
<tr>
<td>IPPV, median days (IQR)</td>
<td>17 (5-31)</td>
<td>0 (0-0)</td>
<td>- |</td>
</tr>
<tr>
<td>Oxygen therapy, median days (IQR)</td>
<td>48 (16-86)</td>
<td>0 (0-0)</td>
<td>- |</td>
</tr>
<tr>
<td>Age at follow-up, years</td>
<td>17.9 (0.8)</td>
<td>18.0 (0.8)</td>
<td>-0.1 (-0.3, 0.06); p=0.19</td>
</tr>
<tr>
<td>zWeight at 18 year follow-up</td>
<td>-0.04 (1.48)</td>
<td>0.46 (1.09)</td>
<td>-0.50 (-0.78, -0.22); p&lt;0.001</td>
</tr>
<tr>
<td>BMI, m(^2)/kg</td>
<td>23.1 (5.1)</td>
<td>22.8 (3.5)</td>
<td>0.3 (-0.7, 1.2); p=0.6</td>
</tr>
<tr>
<td>zBMI at 18 year follow-up</td>
<td>0.28 (1.34)</td>
<td>0.43 (1.06)</td>
<td>-0.14 (-0.43, -0.15); 0.33</td>
</tr>
<tr>
<td>Current asthma, n (%)*</td>
<td>34 (29.3)</td>
<td>19 (23.5)</td>
<td>( \chi^2 (1) = 0.831; p=0.362 )</td>
</tr>
<tr>
<td>Current smokers, n (%)†</td>
<td>16 (13.3)</td>
<td>16 (19.1)</td>
<td>( \chi^2 (1) = 1.220; p=0.269 )</td>
</tr>
</tbody>
</table>

Variables are expressed as mean (SD), unless otherwise stated; *self-reported asthma & Doctor diagnosed asthma & asthma medications; †cigarette smoking exposure
8.1.2 Respiratory function tests

One set of spirometry data was excluded from the EP/ELBW group as it did not reach ATS/ERS standards.(28,33) Lung volume data were available for 66% (198/298) of EP/ELBW subjects and for 55% (143/262) of controls. Eight lung volume results were excluded from the EP/ELBW group and 11 from the controls as they did not meet ATS/ERS standards.(33,38) Two EP/ELBW subjects who had cerebral palsy were not able to complete lung volumes measures due to co-ordination issues. Diffusing capacity data were available for 68% (203/298) of EP/ELBW subjects and 58% (153/262) of controls. Four DLco results from EP/ELBW group and one from the control group were excluded, as they did not reach ATS/ERS standards, one EP/ELBW subject was unable to complete the DLco test due to co-ordination issues.(33,46) MBNW data were available for 26% (77/298) of EP/ELBW subjects and for 20% (52/262) of controls. Eight EP/ELBW subjects and 6 controls had their MBNW data excluded as they did not reach published standards, a further 123 EP/ELBW and 96 controls were not able to complete MBNW tests due to equipment failure, or unavailability.(224) Excluded data is not included in the analysis.

8.1.2.1 Airflow

All spirometry variables, zFEV1, zFEV1/FVC and zFEF25-75%, were significantly reduced in the EP/ELW group compared with the control group (Table 9 and Figure 20). Bronchodilator response (BDR), specific effective airways resistance (sReff) and specific total airways resistance (sRtot) were all significantly elevated compared with controls (Table 9 and Figure 20). Age, height and weight did not contribute to the models for sReff or sRtot.

Table 9: Multiple regression analysis of the relationship between EP/ELBW and lung function measurements reflecting airflow

<table>
<thead>
<tr>
<th>Variable</th>
<th>Explanatory variable</th>
<th>Coefficient</th>
<th>S.E.</th>
<th>95% CI</th>
<th>p-value</th>
<th>R² Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>zFEV1</td>
<td>EP/ELBW</td>
<td>-0.895</td>
<td>0.115</td>
<td>-1.121, -0.669</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>zFEV1/FVC</td>
<td>EP/ELBW</td>
<td>-0.727</td>
<td>0.117</td>
<td>-0.958, -0.496</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>zFEF25-75%</td>
<td>EP/ELBW</td>
<td>-1.121</td>
<td>0.120</td>
<td>-1.357, -0.886</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>BDR, mL*</td>
<td>EP/ELBW</td>
<td>5.45</td>
<td>2.24</td>
<td>1.03, 9.86</td>
<td>p=0.016</td>
<td></td>
</tr>
<tr>
<td>sR eff, kPa.s⁻¹</td>
<td>EP/ELBW</td>
<td>0.205</td>
<td>0.041</td>
<td>0.124, 0.286</td>
<td>p&lt;0.001</td>
<td>10.6%</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td>0.002</td>
<td>0.025</td>
<td>-0.047, 0.050</td>
<td>p=0.942</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>0.101</td>
<td>0.052</td>
<td>-0.002, 0.204</td>
<td>p=0.055</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td></td>
<td>0.001</td>
<td>0.003</td>
<td>-0.005, 0.007</td>
<td>p=0.678</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td>-0.0004</td>
<td>0.002</td>
<td>-0.004, 0.003</td>
<td>p=0.792</td>
<td></td>
</tr>
<tr>
<td>sR tot, kPa.s⁻¹</td>
<td>EP/ELBW</td>
<td>0.210</td>
<td>0.044</td>
<td>0.123, 0.298</td>
<td>p&lt;0.001</td>
<td>9.6%</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td>0.004</td>
<td>0.027</td>
<td>-0.048, 0.057</td>
<td>p=0.873</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>0.109</td>
<td>0.057</td>
<td>-0.002, 0.221</td>
<td>p=0.054</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td></td>
<td>0.0006</td>
<td>0.003</td>
<td>-0.006, 0.007</td>
<td>p=0.851</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td>-0.0003</td>
<td>0.002</td>
<td>-0.004, 0.003</td>
<td>p=0.873</td>
<td></td>
</tr>
</tbody>
</table>

*change in FEV1 post bronchodilator
Figure 20: Distributional dot plots of $zFEV_1$, $zFEV_1/FVC$ and $zFEF_{25-75\%}$ at the 18-year follow-up contrasted between the groups. ••• represents ±1.96 SDs from the mean (limits of normal); ... represents the mean value from the reference set; ---- represents mean z-score for the group.
Figure 21: Distributional dot plots of bronchodilator response (FEV1 mL), effective airways resistance (sReff) and total airways resistance (sRtot) actual values at the 18 year follow-up contrasted between the groups. --- represents the upper limit of normal (1.30kPa.s⁻¹); ---- represents mean value for the group.

Salbutamol 400mcg via metered dose inhaler and volumetric spacer

<table>
<thead>
<tr>
<th></th>
<th>EP/ELBW</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bronchodilator response (mL.s)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>203</td>
<td>151</td>
</tr>
<tr>
<td>Mean</td>
<td>19.2</td>
<td>13.7</td>
</tr>
<tr>
<td>SD</td>
<td>21.0</td>
<td>20.7</td>
</tr>
<tr>
<td><strong>sReff (kPa.s⁻¹)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>179</td>
<td>137</td>
</tr>
<tr>
<td>Mean</td>
<td>1.41</td>
<td>1.21</td>
</tr>
<tr>
<td>SD</td>
<td>0.38</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>sRtot (kPa.s⁻¹)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>179</td>
<td>137</td>
</tr>
<tr>
<td>Mean</td>
<td>1.55</td>
<td>1.34</td>
</tr>
<tr>
<td>SD</td>
<td>0.42</td>
<td>0.29</td>
</tr>
</tbody>
</table>

P<0.001
8.1.2.2 Lung Volumes

The forced vital capacity (zFVC, Table 10 and Figure 22) was significantly reduced in the EP/ELBW group compared with controls. The EP/ELBW group had significantly elevated residual volume (zRV) compared with controls (Table 10 and Figure 22). EP/ELBW did not contribute to the models for either total lung capacity (zTLC, Table 10 and Figure 22) or alveolar volume estimated from the single-breath hold technique used to measure diffusing capacity (zVa, Table 20 and Figure 22). The regression model for TLC with “refset” as an explanatory variable shows the different reference sets used for calculation of zTLC significantly contributed to elevated zTLC, by more than 1½ z-scores (Table 10), this offset from the mean (or zero) is clearly demonstrated in Figure 22, where the mean z-score for the control group has a mean zTLC of 0.92, this ideally should be zero or close to zero. This may be due to cohort effects, i.e. the reference data comes from publications in 1976 (5-18 years) and 1993 (>18 years), and are drawn from subjects tested prior to these dates, the control population in the current study was born in 1991-1992, and therefore comes from a different era. Therefore, analysis of TLC was conducted using age, height, weight and gender as explanatory variables within the model, as per the analysis plan. Neither RV nor Va was more affected by the reference set used in the regression equations, Table 10.

Table 10: Multiple regression analysis of the relationship between EP/ELBW and lung function measurements reflecting lung volumes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Explanatory variable</th>
<th>Coefficient</th>
<th>S.E.</th>
<th>95% CI</th>
<th>p-value</th>
<th>R² Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>zFVC</td>
<td>EP/ELBW</td>
<td>-0.358</td>
<td>0.115</td>
<td>-0.583, -0.132</td>
<td>p=0.002</td>
<td></td>
</tr>
<tr>
<td>zTLC</td>
<td>EP/ELBW</td>
<td>0.192</td>
<td>0.166</td>
<td>-0.135, 0.518</td>
<td>p=0.249</td>
<td>27.3%</td>
</tr>
<tr>
<td></td>
<td>Refset</td>
<td>1.577</td>
<td>0.141</td>
<td>1.299, 1.855</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>zRV</td>
<td>EP/ELBW</td>
<td>0.180</td>
<td>0.057</td>
<td>0.068, 0.292</td>
<td>p=0.002</td>
<td>2.8%</td>
</tr>
<tr>
<td></td>
<td>Refset</td>
<td>-0.071</td>
<td>0.056</td>
<td>-0.181, 0.039</td>
<td>p=0.206</td>
<td></td>
</tr>
<tr>
<td>zVa</td>
<td>EP/ELBW</td>
<td>0.102</td>
<td>0.097</td>
<td>-0.089, 0.292</td>
<td>p=0.293</td>
<td>0.3%</td>
</tr>
<tr>
<td></td>
<td>Refset</td>
<td>0.042</td>
<td>0.154</td>
<td>-0.344, 0.261</td>
<td>p=0.786</td>
<td></td>
</tr>
<tr>
<td>TLC, L</td>
<td>EP/ELBW</td>
<td>0.012</td>
<td>0.074</td>
<td>-0.133, 0.158</td>
<td>p=0.866</td>
<td>74.7%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>0.160</td>
<td>0.045</td>
<td>0.072, 0.249</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>0.769</td>
<td>0.096</td>
<td>0.580, 0.957</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>0.076</td>
<td>0.005</td>
<td>0.065, 0.087</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>-0.001</td>
<td>0.003</td>
<td>-0.007, 0.004</td>
<td>p=0.652</td>
<td></td>
</tr>
</tbody>
</table>

Refset = Reference set used for calculation of TLC z-scores: Zapletal et al. (5-18 years) and Quanjer et al. (18+ years)(287)(288)
Refset = Reference set used for calculation of Va z-scores: Kim et al. (≤ 19 years) and American Thoracic Society (> 19 years)(63,67)(63)
Figure 22: Distributional dot plots of zFVC, zTLC, zRV and zVA at the 18 year follow-up contrasted between the groups. ---- represents ±1.96 SDs from the mean (limits of normal); ... represents the mean value from the reference set; ----- represents mean z-score for the group.

<table>
<thead>
<tr>
<th></th>
<th>FVC z-score</th>
<th>TLC z-score</th>
<th>RV z-score</th>
<th>VA z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>EP/ELBW</td>
<td>Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=208</td>
<td>Mean=-0.36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD=1.14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=153</td>
<td>Mean=-0.0009</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD=0.98</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p=0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>FVC z-score</th>
<th>TLC z-score</th>
<th>RV z-score</th>
<th>VA z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>EP/ELBW</td>
<td>Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=202</td>
<td>Mean=1.13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD=0.91</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=152</td>
<td>Mean=0.92</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD=0.70</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>FVC z-score</th>
<th>TLC z-score</th>
<th>RV z-score</th>
<th>VA z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>EP/ELBW</td>
<td>Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=202</td>
<td>Mean=0.90</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD=0.53</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=152</td>
<td>Mean=0.70</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD=0.51</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>FVC z-score</th>
<th>TLC z-score</th>
<th>RV z-score</th>
<th>VA z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>EP/ELBW</td>
<td>Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=202</td>
<td>Mean=-0.21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD=0.91</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=152</td>
<td>Mean=-0.30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD=0.79</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
8.1.2.3 Diffusing capacity

The diffusing capacity of the lung (zDLCO, Table 11 and Figure 23) was significantly reduced, even after adjusted for alveolar volume (zDLCO/Va, Table 11 and Figure 23), in the EP/ELBW group compared with the control group. Again there are two sets of reference equations used to calculate the z-scores for DLCO and DLCO/Va, Kim et al. were used to calculate z-scores for those ≤19 years of age and the American Thoracic Society equations were used for those >19 years of age. “Refset” showed no effect on zDLCO or zDLCO/Va (Table 11), and therefore no further analysis of DLCO used “refset” in the model.

Table 11: EP/ELBW adjusted regression coefficients – Diffusing capacity

<table>
<thead>
<tr>
<th>Variable</th>
<th>Explanatory variable</th>
<th>Coefficient</th>
<th>S.E.</th>
<th>95% CI</th>
<th>p-value</th>
<th>R² Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>zDLCO</td>
<td>EP/ELBW</td>
<td>-0.458</td>
<td>0.105</td>
<td>-0.666, -0.251</td>
<td>p&lt;0.001</td>
<td>4.9%</td>
</tr>
<tr>
<td></td>
<td>Refset</td>
<td>0.093</td>
<td>0.167</td>
<td>-0.236, 0.422</td>
<td>p=0.579</td>
<td></td>
</tr>
<tr>
<td>zDLCO/Va</td>
<td>EP/ELBW</td>
<td>-0.613</td>
<td>0.096</td>
<td>-0.802, -0.424</td>
<td>p=0.001</td>
<td>10.6%</td>
</tr>
<tr>
<td></td>
<td>Refset</td>
<td>0.163</td>
<td>0.153</td>
<td>-0.138, 0.462</td>
<td>p=0.287</td>
<td></td>
</tr>
</tbody>
</table>

Refset = Reference set used for calculation of z-scores: Kim et al. (≤ 19 years; coded as 1 in the model) and American Thoracic Society (> 19 years; coded as 0 in the model) (63, 67)
Figure 23: Distributional dot plots of zDLCO and zDLCO/Va at the 18 year follow-up contrasted between the groups. - - - represents ±1.96 SDs from the mean (limits of normal) ... represents the mean value from the reference set; --- represents mean z-score for the group.

<table>
<thead>
<tr>
<th></th>
<th>EP/ELBW</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>202</td>
<td>152</td>
</tr>
<tr>
<td>Mean</td>
<td>-0.47</td>
<td>0.0006</td>
</tr>
<tr>
<td>SD</td>
<td>0.92</td>
<td>0.96</td>
</tr>
</tbody>
</table>

p<0.001

<table>
<thead>
<tr>
<th></th>
<th>EP/ELBW</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>202</td>
<td>152</td>
</tr>
<tr>
<td>Mean</td>
<td>-0.82</td>
<td>-0.20</td>
</tr>
<tr>
<td>SD</td>
<td>0.81</td>
<td>0.90</td>
</tr>
</tbody>
</table>

p<0.001
8.1.2.4 Ventilation efficiency

Ventilation efficiency within the lungs, (zLCI) was similar in the EP/ELBW group and controls. A determinant of ventilation efficiency within the acinar zone (Sacin) was male gender, being higher in males, which relates to worsening ventilation efficiency. EP/ELBW was associated with increased ventilation inefficiency within the conducting zone of the lungs (Scond). Table 12 and Figure 24 display the results for ventilation efficiency.

Table 12: EP/ELBW adjusted regression coefficients – Ventilation efficiency

<table>
<thead>
<tr>
<th>Variable</th>
<th>Explanatory variable</th>
<th>Coefficient</th>
<th>S.E.</th>
<th>95% CI</th>
<th>p-value</th>
<th>R² Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>zLCI</td>
<td>EP/ELBW</td>
<td>-0.448</td>
<td>0.342</td>
<td>-1.124, 0.229</td>
<td>p=0.193</td>
<td></td>
</tr>
<tr>
<td>Sacin, L¹</td>
<td>EP/ELBW</td>
<td>-0.029</td>
<td>0.026</td>
<td>-0.082, 0.023</td>
<td>p=0.270</td>
<td>6.0%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>-0.020</td>
<td>0.020</td>
<td>-0.060, 0.020</td>
<td>p=0.330</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>0.094</td>
<td>0.034</td>
<td>0.026, 0.162</td>
<td>p=0.007</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>-0.002</td>
<td>0.002</td>
<td>-0.006, 0.002</td>
<td>p=0.411</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>-0.0007</td>
<td>0.001</td>
<td>-0.003, 0.002</td>
<td>p=0.523</td>
<td></td>
</tr>
<tr>
<td>Scond, L¹</td>
<td>EP/ELBW</td>
<td>0.016</td>
<td>0.005</td>
<td>0.006, 0.026</td>
<td>p=0.003</td>
<td>6.0%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>0.002</td>
<td>0.004</td>
<td>-0.006, 0.010</td>
<td>p=0.597</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>0.009</td>
<td>0.007</td>
<td>-0.004, 0.022</td>
<td>p=0.174</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>-0.00002</td>
<td>0.0004</td>
<td>-0.0009, 0.0006</td>
<td>p=0.673</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>-0.0001</td>
<td>0.0002</td>
<td>-0.0006, 0.0003</td>
<td>p=0.580</td>
<td></td>
</tr>
</tbody>
</table>
Figure 24: Distributional dot plots of zLCl, Sacin and Scond at the 18 year follow-up contrasted between the groups. -- represents ±1.96 SDs from the mean (limits of normal) ... represents the mean value from the reference set; --- represents mean value for the group.

- LCl z-score

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>75</td>
<td>0.33</td>
<td>2.03</td>
</tr>
<tr>
<td>EP/ELBW</td>
<td>51</td>
<td>0.78</td>
<td>1.64</td>
</tr>
</tbody>
</table>

- Sacin (L^-1)

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>74</td>
<td>0.169</td>
<td>0.130</td>
</tr>
<tr>
<td>EP/ELBW</td>
<td>51</td>
<td>0.199</td>
<td>0.145</td>
</tr>
</tbody>
</table>

- Scond (L^-1)

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>75</td>
<td>0.033</td>
<td>0.029</td>
</tr>
<tr>
<td>EP/ELBW</td>
<td>51</td>
<td>0.018</td>
<td>0.021</td>
</tr>
</tbody>
</table>

p=0.002
8.1.3 Cardiopulmonary exercise

Cardiopulmonary exercise was attempted on 84% (175/208) of EP/ELBW subjects and 86% (132/153) controls who attended for the 18-year follow-up. Thirty-three EP/ELBW subjects and 21 controls did not attempt cardiopulmonary exercise, this was mainly due to equipment issues, but some were not tested because they had inappropriate clothing or shoes (n=5), one control subject and 3 EP/ELBW subjects had asthma that was significant enough to mean exercise was unsafe, four EP/ELBW subjects had cerebral palsy and were unsafe to use the treadmill, two EP/ELBW subjects ended the test early due to a sore throat, 3 EP/ELBW subjects had orthopaedic issues that prevented them from achieving maximal exercise (sore ankle from previous fracture, arthritic knee and right hip avascular necrosis), one EP/ELBW subject was diabetic and had not eaten appropriately to complete an exercise test, and 1 EP/ELBW subject had severe intra-thoracic airflow obstruction on spirometry with severe stridor and it was not considered safe to exercise them. Of those who attempted to exercise, 33 EP/ELBW and 6 control sets of cardiopulmonary data were excluded from the analysis as they did not reach >1.05 for respiratory exchange ratio and >90% of their predicted HRmax, indicating a sub-maximal effort, and included tests that were prematurely ended due to equipment failure during the test, clothing failure during the test or scientist concerns for the safety for the participant that resulted in early termination of the exercise test, or deconditioning.

This meant that cardiopulmonary exercise was successfully measured on 48% (142/298) EP/ELBW and 48% (126/262) controls.

8.1.3.1 Metabolic rate

EP/ELBW was a significant contributor to the maximal work rate achieved (Table 13 and Figure 25), where being EP or ELBW reduced the work rate maximum by over 200 Watts. In addition, as expected, sex (by approximately 400 Watts for males), height (by approximately 8 Watts per cm increasing height) and weight (by approximately 8 Watts per kg increasing weight) all had positive influences within the model. Age did not significantly influence the model.

The V'O₂/Work relationship (Table 13 and Figure 25) was increased in the EP/ELBW subjects compared with controls, i.e. the amount of oxygen consumption per given work rate was increased in EP/ELBW, by 0.4 mL.min.W⁻¹. As expected, V'O₂/Work at maximal exercise decreased with increasing weight, by approximately 0.02 mL.min.W⁻¹ per kg increase in weight. Sex, age and height did not significantly contribute to the model.
Table 13: Cardiopulmonary EP/ELBW exercise adjusted coefficients

<table>
<thead>
<tr>
<th>Cardiopulmonary variable</th>
<th>Explanatory variable</th>
<th>Coefficient</th>
<th>S.E.</th>
<th>95% CI</th>
<th>p-value</th>
<th>R^2 Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Workmax, W</td>
<td>EP/ELBW</td>
<td>-203.1</td>
<td>51.9</td>
<td>-305.3, -100.9</td>
<td>p&lt;0.001</td>
<td>44.2%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>-26.9</td>
<td>31.0</td>
<td>-87.9, 34.2</td>
<td>p=0.387</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>410.3</td>
<td>68.4</td>
<td>275.6, 545.1</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>8.2</td>
<td>4.0</td>
<td>0.3, 16.1</td>
<td>p=0.043</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>8.9</td>
<td>2.1</td>
<td>4.8, 13.0</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>V'O2/Work, mL.min.W^{-1}</td>
<td>EP/ELBW</td>
<td>0.406</td>
<td>0.175</td>
<td>0.062, 0.750</td>
<td>p=0.021</td>
<td>8.1%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>-0.023</td>
<td>0.106</td>
<td>-0.213, 0.185</td>
<td>p=0.826</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>-0.342</td>
<td>0.230</td>
<td>-0.795, 0.111</td>
<td>p=0.138</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>-0.007</td>
<td>0.013</td>
<td>-0.033, 0.020</td>
<td>p=0.611</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>-0.016</td>
<td>0.007</td>
<td>-0.030, -0.002</td>
<td>p=0.026</td>
<td></td>
</tr>
</tbody>
</table>

Figure 25: Distributional dot plots of maximal work rate actual values at the 18 year follow-up contrasted between the EP/ELBW and control groups. ___ represents mean value for the group.
8.1.3.2 Cardiovascular function

As expected, maximal heart rate achieved (Table 14 and Figure 26) decreased with increasing age (by approximately 2 beats per year of age). This could reflect the predicted maximum heart rate achievable which was calculated from 220-age, which uses age as the reducing factor. Gender, height, weight and EP/ELBW did not contribute to the model. EP/ELBW had no effect on maximal heart rate achieved.

EP/ELBW subjects had a reduced O₂pulse (Table 14 and Figure 26) at maximal exercise compared with controls, by approximately 1mL.beat⁻¹ for EP/ELBW subjects. Gender (by approximately 3 mL.beat⁻¹ in males) and weight (by approximately 0.1mL.beat⁻¹ per kg increasing weight) had small but significant associations on the maximal O₂pulse. Age and height did not significantly contribute to the model.

Table 14: Cardiopulmonary EP/ELBW exercise adjusted coefficients

<table>
<thead>
<tr>
<th>Cardiopulmonary variable</th>
<th>Explanatory variable</th>
<th>Coefficient</th>
<th>S.E.</th>
<th>95% CI</th>
<th>p-value</th>
<th>R² Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>( HR_{max}, \text{beats.min}^{-1} )</td>
<td>EP/ELBW</td>
<td>-0.87</td>
<td>1.22</td>
<td>-3.28, 1.53</td>
<td>p=0.475</td>
<td>2.9%</td>
</tr>
<tr>
<td>( \text{Age (years)} )</td>
<td></td>
<td>-2.13</td>
<td>0.73</td>
<td>-3.57, -0.70</td>
<td>p=0.004</td>
<td></td>
</tr>
<tr>
<td>( \text{Male} )</td>
<td></td>
<td>2.75</td>
<td>1.60</td>
<td>-0.41, 5.91</td>
<td>p=0.088</td>
<td></td>
</tr>
<tr>
<td>( \text{Height (cm)} )</td>
<td></td>
<td>-0.05</td>
<td>0.09</td>
<td>-0.23, 0.14</td>
<td>p=0.617</td>
<td></td>
</tr>
<tr>
<td>( \text{Weight (kg)} )</td>
<td></td>
<td>0.02</td>
<td>0.05</td>
<td>-0.07, 0.01</td>
<td>p=0.629</td>
<td></td>
</tr>
<tr>
<td>( O₂\text{Pulse, mL.beat}^{-1} )</td>
<td>EP/ELBW</td>
<td>-0.918</td>
<td>0.404</td>
<td>-1.714, -0.122</td>
<td>p=0.024</td>
<td>41.2%</td>
</tr>
<tr>
<td>( \text{Age (years)} )</td>
<td></td>
<td>-0.053</td>
<td>0.244</td>
<td>-0.533, 0.428</td>
<td>p=0.829</td>
<td></td>
</tr>
<tr>
<td>( \text{Male} )</td>
<td></td>
<td>2.777</td>
<td>0.531</td>
<td>1.732, 3.823</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>( \text{Height (cm)} )</td>
<td></td>
<td>0.006</td>
<td>0.031</td>
<td>-0.055, 0.068</td>
<td>p=0.838</td>
<td></td>
</tr>
<tr>
<td>( \text{Weight (kg)} )</td>
<td></td>
<td>0.122</td>
<td>0.017</td>
<td>0.089, 0.155</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>( SV\text{ at AT, mL} )</td>
<td>EP/ELBW</td>
<td>-18.7</td>
<td>5.6</td>
<td>-29.9, -7.6</td>
<td>p=0.001</td>
<td>35.5%</td>
</tr>
<tr>
<td>( \text{Age (years)} )</td>
<td></td>
<td>-5.0</td>
<td>3.3</td>
<td>-11.6, 1.6</td>
<td>p=0.133</td>
<td></td>
</tr>
<tr>
<td>( \text{Male} )</td>
<td></td>
<td>-3.1</td>
<td>7.4</td>
<td>-17.9, 11.7</td>
<td>p=0.676</td>
<td></td>
</tr>
<tr>
<td>( \text{Height (cm)} )</td>
<td></td>
<td>0.8</td>
<td>0.4</td>
<td>0.04, 1.6</td>
<td>p=0.040</td>
<td></td>
</tr>
<tr>
<td>( \text{Weight (kg)} )</td>
<td></td>
<td>0.8</td>
<td>0.2</td>
<td>0.4, 1.2</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>( \text{Haemoglobin, g.L}^{-1} )</td>
<td>EP/ELBW</td>
<td>3.9</td>
<td>0.16</td>
<td>0.7, 0.712</td>
<td>p=0.017</td>
<td>65.4%</td>
</tr>
<tr>
<td>( \text{Male} )</td>
<td></td>
<td>23.9</td>
<td>0.16</td>
<td>20.7, 2.7</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>( \text{Age} )</td>
<td></td>
<td>1.4</td>
<td>0.10</td>
<td>-0.5, 0.339</td>
<td>p=0.147</td>
<td></td>
</tr>
</tbody>
</table>

EP/ELBW subjects had reduced stroke volume at the ventilatory threshold, also known as anaerobic threshold (by approximately 19mL for EP/ELBW) compared with controls.

Not all subjects had their haemoglobin measured due to refusal of the blood test required, haemoglobin results were obtained on 32% (66/208) EP/ELBW subjects who had mean haemoglobin of 139 g.L⁻¹ (range, 116 to 177 g.L⁻¹) and 52% (79/153) controls with a mean haemoglobin 146 g.L⁻¹ (range, 109 to 179 g.L⁻¹), therefore stroke volume at Vt is only calculated for these subjects (Table 14).
Figure 26: Distributional dot plots of maximal heart rate values at the 18 year follow-up contrasted between the EP/ELBW and control groups. ___ represents mean value for the group.
### Ventilatory function

Maximal ventilation (Table 15 and Figure 27) was significantly higher in males, which could reflect larger lung volumes in males. Weight had a significant association with maximal ventilation (by approximately 35mL per kg increasing weight). There were no associations between height, age or EP/ELBW and maximal ventilation.

As expected, breathing frequency (Table 15 and Figure 27) or respiratory rate decreased with increasing height (by approximately 0.5 breaths.min⁻¹ per cm increasing height), which could reflect increasing lung volume with height. There was no association between weight, age or EP/ELBW and maximal breathing frequency.

The major determinants of Vtmax (Table 15 and Figure 27) were height (by approximately 24 mL per cm increasing height), weight (by approximately 6 mL per kg increasing weight) and gender (by approximately 189 mL for males). This could reflect increasing lung volume with growth in the age groups involved in this study and increased lung volumes in males. There was no association between age or EP/ELBW and maximal tidal volume achieved.

Maximal inspiratory duty cycle (Ti/Ttot, Table 15 and Figure 27) was significantly associated with age, where each year increased age is associated with an increased Ti/Ttot ratio of approximately 0.5, i.e. decreasing inspiratory time as a component of total tidal volume, or the portion of respiration when the inspiratory muscles are active and will show an alterations in ventilatory timing. There was no association between EP/ELBW, gender, height or weight and Ti/Ttot in the model.

EP/ELBW subjects used a higher percentage of their ventilatory reserve (V'E/MVV, Table 15 and Figure 27), by approximately 4% in the EP/ELBW group compared with controls, which could reflect abnormal static lung function variables, such as reduced FEV₁ and elevated RV. Male subjects used a higher percentage of their V'E/MVV, by approximately 8% compared with females, this may relate to the higher maximal V'E rate and V'O₂max achieved (Table 15). Height was a small but significant contributor to the model, by approximately 0.7% per cm increase in height.
<table>
<thead>
<tr>
<th>Cardiopulmonary variable</th>
<th>Explanatory variable</th>
<th>Coefficient</th>
<th>S.E.</th>
<th>95% CI</th>
<th>p-value</th>
<th>R² Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>V'Emax, L.min&lt;sup&gt;1&lt;/sup&gt;</td>
<td>EP/ELBW</td>
<td>-4.37</td>
<td>2.29</td>
<td>-8.88, 0.14</td>
<td>p=0.057</td>
<td>39.5%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>-1.79</td>
<td>1.38</td>
<td>-4.49, 0.92</td>
<td>p=0.194</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>18.68</td>
<td>3.02</td>
<td>12.73, 24.63</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>0.27</td>
<td>0.18</td>
<td>-0.08, 0.62</td>
<td>p=0.124</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>0.35</td>
<td>0.09</td>
<td>0.17, 0.53</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>BFmax, breaths.min&lt;sup&gt;1&lt;/sup&gt;</td>
<td>EP/ELBW</td>
<td>-0.84</td>
<td>1.19</td>
<td>-3.18, 1.50</td>
<td>p=0.482</td>
<td>8.3%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>-1.01</td>
<td>0.71</td>
<td>-2.41, 0.39</td>
<td>p=0.158</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>5.81</td>
<td>1.57</td>
<td>2.72, 8.90</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>-0.46</td>
<td>0.09</td>
<td>-0.64, -0.28</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>0.04</td>
<td>0.05</td>
<td>-0.05, 0.13</td>
<td>p=0.380</td>
<td></td>
</tr>
<tr>
<td>Vtmax, L</td>
<td>EP/ELBW</td>
<td>-0.069</td>
<td>0.049</td>
<td>-0.165, 0.028</td>
<td>p=0.162</td>
<td>47.7%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>0.021</td>
<td>0.029</td>
<td>-0.037, 0.079</td>
<td>p=0.484</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>0.189</td>
<td>0.065</td>
<td>0.062, 0.032</td>
<td>p=0.004</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>0.024</td>
<td>0.004</td>
<td>0.016, 0.031</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>0.006</td>
<td>0.002</td>
<td>0.002, 0.010</td>
<td>p=0.002</td>
<td></td>
</tr>
<tr>
<td>Ti/Ttot</td>
<td>EP/ELBW</td>
<td>0.618</td>
<td>0.385</td>
<td>-0.139, 1.376</td>
<td>p=0.109</td>
<td>2.7%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>0.524</td>
<td>0.231</td>
<td>0.068, 0.980</td>
<td>p=0.024</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>-0.505</td>
<td>0.507</td>
<td>-1.504, 0.493</td>
<td>p=0.320</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>-0.016</td>
<td>0.015</td>
<td>-0.046, 0.014</td>
<td>p=0.291</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>-0.0009</td>
<td>0.030</td>
<td>-0.059, 0.058</td>
<td>p=0.977</td>
<td></td>
</tr>
<tr>
<td>V'E/MVV, %</td>
<td>EP/ELBW</td>
<td>3.807</td>
<td>1.821</td>
<td>0.221, 7.394</td>
<td>p=0.038</td>
<td>12.1%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>-1.86</td>
<td>1.09</td>
<td>-4.007, 0.295</td>
<td>p=0.090</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>8.193</td>
<td>2.410</td>
<td>3.447, 12.940</td>
<td>p=0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>-0.664</td>
<td>0.142</td>
<td>-0.943, -0.385</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>0.135</td>
<td>0.073</td>
<td>-0.008, 0.278</td>
<td>p=0.064</td>
<td></td>
</tr>
</tbody>
</table>
Figure 27: Distributional dot plots of maximal minute ventilation (V’Emax), breathing frequency (BF), maximal tidal volume (Vtmax), maximal inspiratory duty cycle (Ti/Ttot) and maximal respiratory reserve (V’E/MVV) actual values at the 18 year follow-up contrasted between the EP/ELBW and control groups. ___ represents mean value for the group.
8.1.3.4 Gas exchange

The $V'O_2\text{max}$ (Table 16 and Figure 28) was significantly reduced in the EP/ELBW group compared with controls, by approximately 195 mL.min$^{-1}$ for EP/ELBW subjects. As expected, $V'O_2\text{max}$ increased with increasing height (by approximately 13 mL.min$^{-1}$ per cm increasing height), and increasing weight (by approximately 18 mL.min$^{-1}$ per kg increasing weight) and was also higher in males, by approximately 530 mL.min$^{-1}$. Age did not contribute to the model. When $V'O_2\text{max}$ was adjusted for body weight (mL.min.kg$^{-1}$, Table 17 and Figure 28) it was significantly reduced in EP/ELBW subjects compared with controls. $V'O_2\text{max}$ adjusted for body weight slightly increased with increasing height (by approximately 0.2 mL.min.kg$^{-1}$ per cm increasing height), it decreased slightly with increasing weight (by approximately 0.3 mL.min.kg$^{-1}$ per kg increasing weight) and was also higher in males. Age did not contribute to the model.

None of the factors included in the model for maximal oxygen saturation ($SpO_2$, Table 16 and Figure 28) showed any significant contributions; hence the Adjusted $R^2$ for this model is 0.7%.

The $VCO_2\text{max}$ (Table 16 and Figure 28) was significantly reduced in the EP/ELBW group compared with controls, by approximately 200 mL.min$^{-1}$ for EP/ELBW subjects. As expected, $VCO_2\text{max}$ increased with increasing height (by approximately 13 mL.min$^{-1}$ per cm increasing height), and increasing weight (by approximately 23 mL.min$^{-1}$ per kg increasing weight) and was also higher in males, by approximately 640 mL.min$^{-1}$. Age did not contribute to the model.

The major determinant of ventilatory equivalent for O$_2$ and CO$_2$ in the models (Table 16 and Figure 28) was weight, with both $V'E/V'O_2$ and $V'E/V'O_2$ increasing by approximately 0.1 unit per kg increase in weight, which may reflect the influence of weight on peak ventilation, suggesting higher ventilation rates at peak exercise in heavier subjects. EP/ELBW, gender, age and height did not significantly contribute to the model.

Male sex was significantly associated with a small but significant increase in the fraction expired CO$_2$ ($FETCO_2$, Table 16) level at peak exercise, which may relate to the influence of gender on $V'CO_2$. 

### Table 16: Cardiopulmonary EP/ELBW exercise adjusted coefficients

<table>
<thead>
<tr>
<th>Cardiopulmonary variable</th>
<th>Explanatory variable</th>
<th>Coefficient</th>
<th>S.E.</th>
<th>95% CI</th>
<th>p-value</th>
<th>R² Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V'O_2 \text{max, mL.min}^-1 )</td>
<td>EP/ELBW</td>
<td>-195.1</td>
<td>59.5</td>
<td>-312.4, -77.8</td>
<td>p=0.001</td>
<td>57.7%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>-36.4</td>
<td>36.0</td>
<td>-107.3, 34.6</td>
<td>p=0.314</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>530.9</td>
<td>78.4</td>
<td>376.5, 685.3</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>12.8</td>
<td>4.6</td>
<td>3.8, 21.9</td>
<td>p=0.006</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>17.7</td>
<td>2.4</td>
<td>12.9, 22.4</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>( V'O_2 \text{max, mL.min.kg}^-1 )</td>
<td>EP/ELBW</td>
<td>-2.83</td>
<td>0.90</td>
<td>-4.59, -1.06</td>
<td>p=0.002</td>
<td>37.9%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>-0.63</td>
<td>0.54</td>
<td>-1.70, 0.44</td>
<td>p=0.248</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>8.20</td>
<td>1.18</td>
<td>5.87, 10.53</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>0.16</td>
<td>0.07</td>
<td>0.02, 0.29</td>
<td>p=0.024</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>-0.27</td>
<td>0.04</td>
<td>-0.34, -0.19</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>( \text{SpO}_2 \text{max, %} )</td>
<td>EP/ELBW</td>
<td>-0.18</td>
<td>0.29</td>
<td>-0.75, 0.38</td>
<td>p=0.526</td>
<td>0.7%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>-0.10</td>
<td>0.17</td>
<td>-0.43, 0.24</td>
<td>p=0.580</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>-0.04</td>
<td>0.38</td>
<td>-0.79, 0.70</td>
<td>p=0.909</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>0.007</td>
<td>0.02</td>
<td>-0.04, 0.05</td>
<td>p=0.756</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>-0.02</td>
<td>0.01</td>
<td>-0.04, 0.006</td>
<td>p=0.151</td>
<td></td>
</tr>
<tr>
<td>( V'CO_2 \text{max, mL.min}^-1 )</td>
<td>EP/ELBW</td>
<td>-203.0</td>
<td>71.6</td>
<td>-344.1, -61.9</td>
<td>p=0.005</td>
<td>57.3%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>-6.37</td>
<td>43.2</td>
<td>-91.4, 78.6</td>
<td>p=0.883</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>642.9</td>
<td>94.3</td>
<td>457.2, 828.7</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>12.6</td>
<td>5.5</td>
<td>1.7, 23.5</td>
<td>p=0.024</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>23.3</td>
<td>2.9</td>
<td>17.6, 29.0</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>( \text{Ve} / V'O_2 )</td>
<td>EP/ELBW</td>
<td>-0.955</td>
<td>0.616</td>
<td>-2.169, 0.259</td>
<td>p=0.123</td>
<td>8.6%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>0.032</td>
<td>0.372</td>
<td>-0.702, 0.766</td>
<td>p=0.932</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>0.339</td>
<td>0.812</td>
<td>-1.259, 1.938</td>
<td>p=0.676</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>0.048</td>
<td>0.048</td>
<td>-0.045, 0.142</td>
<td>p=0.311</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>0.078</td>
<td>0.025</td>
<td>0.029, 0.127</td>
<td>p=0.002</td>
<td></td>
</tr>
<tr>
<td>( \text{Ve} / V'CO_2 )</td>
<td>EP/ELBW</td>
<td>-0.680</td>
<td>0.682</td>
<td>-2.023, 0.664</td>
<td>p=0.320</td>
<td>12.9%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>0.471</td>
<td>0.411</td>
<td>-0.338, 1.281</td>
<td>p=0.253</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>0.719</td>
<td>0.898</td>
<td>-1.050, 2.488</td>
<td>p=0.424</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>0.050</td>
<td>0.053</td>
<td>-0.053, 0.154</td>
<td>p=0.342</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>0.112</td>
<td>0.028</td>
<td>0.057, 0.167</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>( \text{FETCO}_2 \text{, kPa} )</td>
<td>EP/ELBW</td>
<td>-0.106</td>
<td>0.083</td>
<td>-0.270, 0.058</td>
<td>p=0.204</td>
<td>0.214</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>-0.045</td>
<td>0.050</td>
<td>-0.144, 0.054</td>
<td>p=0.367</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>0.260</td>
<td>0.109</td>
<td>0.044, 0.476</td>
<td>p=0.018</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>0.0004</td>
<td>0.006</td>
<td>-0.012, 0.013</td>
<td>p=0.949</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>0.019</td>
<td>0.003</td>
<td>0.012, 0.026</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>
Figure 28: Distributional dot plots of maximal oxygen consumption (V'O₂max), maximal oxygen consumption per kg (V'O₂max/kg), maximal oxygen saturation (SpO₂), maximal carbon dioxide production (VCO₂max), maximal ventilatory equivalent for O₂ (V'E/V'O₂), maximal ventilatory equivalent for CO₂ (V'E/V'CO₂) actual values at the 18 year follow-up contrasted between the EP/ELBW and control groups. ___ represents mean value for the group.
8.1.3.5 Metabolic acidosis

The $V'O_2$ achieved at the ventilatory threshold (Table 17 and Figure 29) was significantly reduced in the EP/ELBW group compared with controls, by approximately 180 mL.min$^{-1}$ for EP/ELBW subjects, which may reflect deconditioning in the EP/ELBW group. As expected, $V'O_2$ at the ventilatory threshold increased with increasing height (by approximately 13 mL.min$^{-1}$ per cm increasing height), and increasing weight (by approximately 14 mL.min$^{-1}$ per kg increasing weight) and was also higher in males, by approximately 294 mL.min$^{-1}$. Age did not contribute to the model. These overall patterns for $V'O_2$ achieved at the ventilatory threshold reflect those of the $V'O_2$max.

Table 17: Cardiopulmonary EP/ELBW exercise adjusted coefficients

<table>
<thead>
<tr>
<th>Cardiopulmonary variable</th>
<th>Explanatory variable</th>
<th>Coefficient</th>
<th>S.E.</th>
<th>95% CI</th>
<th>p-value</th>
<th>$R^2$ Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V'O_2$ at AT, mL.min$^{-1}$</td>
<td>EP/ELBW</td>
<td>-183.6</td>
<td>64.9</td>
<td>-311.5, -55.7</td>
<td>p=0.005</td>
<td>40.0%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>-3.1</td>
<td>39.1</td>
<td>-80.1, 74.0</td>
<td>p=0.937</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>294.3</td>
<td>85.6</td>
<td>125.7, 462.9</td>
<td>p=0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>13.2</td>
<td>5.0</td>
<td>33.3, 23.1</td>
<td>p=0.009</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>14.6</td>
<td>2.6</td>
<td>9.4, 19.7</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Figure 29: Distributional dot plot maximal oxygen consumption at the ventilatory threshold actual values at the 18 year follow-up contrasted between the EP/ELBW and control groups. _ _ represents mean $V'O_2$ at ventilatory threshold for the group.
8.1.4 Summary of results EP/ELBW compared with controls

There were no differences in gender distribution between EP/ELBW and controls. There were no significance differences in the proportions of EP/ELBW subjects compared with controls who reported asthma or current smoking. Of the EP/ELBW group, 21% were small for gestational age at birth, of which 23% had BPD, whereas no NBW controls were SGA. Within the EP/ELBW group, there were no substantial differences in perinatal data between those tested and not tested at this follow-up. Height and weight were measured at the 18 year follow-up and were significantly reduced in the EP/ELBW group, although there was no difference in the actual BMI or zBMI, suggesting a proportional reduction in both height and weight compared with controls.

Spirometry was successfully measured on 70% EP/ELBW subjects and 58% controls. One set of spirometry data was excluded from the controls, as it did not reach ATS/ERS standards. Lung volumes data were available for 66% EP/ELBW subjects and for 55% controls. Diffusing capacity data were available for (68%) EP/ELBW subjects and 58% controls. MBNW data were available for 26% EP/ELBW subjects and 20% controls.

All spirometry variables were significantly reduced in the EP/ELBW group compared with the control group. Specific effective airways resistance ($sR_{eff}$), specific total airways resistance ($sR_{tot}$) and bronchodilator response (BDR) were all significantly elevated compared with controls.

The EP/ELBW group had significantly elevated residual volume compared with controls.

The diffusing capacity of the lung was significantly reduced, even when adjusted by alveolar volume, in the EP/ELBW group compared with the controls.

There were no significant differences in the selected variables reflecting global and acinar lung zone ventilation efficiency, ($zLCI$; $Sacin$) when comparing the EP/ELBW group with controls. EP/ELBW subjects had an elevated (abnormal) ventilation efficiency within the conducting zones of the lung compared with controls.

Cardiopulmonary exercise testing was successfully measured on 81% of EP/ELBW subjects and 95% of controls, who had other respiratory function testing.

The EP/ELBW subjects had significantly reduced maximal work rate and an increased cost of this work, i.e. the amount of O$_2$ consumption per given watt of work was higher in the EP/ELBW group compared with controls.

The EP/ELBW group had a reduced maximal O$_2$ pulse, i.e. the amount of O$_2$ delivered per heart beat was lower in the EP/ELBW subjects than controls. The EP/ELBW group had reduced stroke volume calculated at the ventilatory (anaerobic) threshold, meaning cardiac output may be reduced in the EP/ELBW group compared with control.
The EP/ELBW group used more of their ventilatory reserve, also known as respiratory reserve compared with controls. There were no differences between the groups for maximal ventilation, breathing frequency, tidal volume or inspiratory duty cycle.

The \( V'\text{O}_2\text{ max} \) was significantly reduced in the EP/ELBW group, even when adjusted for weight, \( V'\text{O}_2\text{ max} \) was also reduced at the ventilatory threshold, suggestive of deconditioning, when compared with control subjects. EP/ELBW subjects also had significantly reduced \( V'\text{CO}_2\text{max} \) when compared to controls. There were no differences between the group’s SpO\(_2\), ventilatory equivalents for O\(_2\) and CO\(_2\) or the fractional expired CO\(_2\) at maximal exercise.

Interestingly, 15 EP/ELBW and 2 control subjects developed co-ordination issues or “wobbly legs” near the end of the exercise test, 2 EP/ELBW subjects had their exercise tests prematurely stopped due to safety concerns related to their co-ordination and increased risk of falling or tripping on the treadmill. There were no differences in gender (\( \chi^2 (1) = 2.94; p=0.09 \)), and amongst the EP/ELBW there was no association with “wobbly legs” and BPD status (\( \chi^2 (1) = 1.91; p=0.17 \)), days of ventilation (\( z=-1.19; p=0.41 \)), days of oxygen (\( z=-1.01; p=0.42 \)), birth weight (\(-533.3 \text{ g}; p=0.09 \)), birth weight z-score (\(-0.28 \text{ z-score}; p=0.67 \)) or gestational age (0.15 weeks’; \( p=0.78 \)). Four EP/ELBW subjects with so called “wobbly legs” were excluded from the analysis of cardiopulmonary exercise as they did not reach 90% or their maximum predicted heart rate and their respiratory exchange ratio was not greater than 1.05, both of which suggest they did not perform a maximal cardiopulmonary exercise test. There was also no association between “wobbly legs” and peak \( V'O_2 \) (-199.6 mL.min\(^{-1}\); \( p=0.34 \)) or heart rate (-1.4 bpm; \( p=0.62 \)) achieved in the EP/ELBW group who were analysed, although the numbers are very small (EP/ELBW n=10; control n=2).
8.2  Respiratory function and exercise capacity at 18 years of age in the EP/ELBW survivors, comparing BPD with no BPD

8.2.1  Population characteristics

Table 18 compares perinatal data of subjects within the EP/ELBW group who had and who did not have BPD and were tested at the 18-year follow-up. The BPD subjects had significantly reduced birth weights and gestational ages at birth than those without BPD, but there was no significant difference between the groups for birth weight z-score. As expected, based on BPD being defined as O₂ requirement beyond 36 weeks, those in the BPD group had significantly higher duration of IPPV and days of O₂ (BPD median 99 vs. No BPD median 28 days; p<0.001).

<table>
<thead>
<tr>
<th>Variable</th>
<th>BPD n = 73</th>
<th>No BPD N = 135</th>
<th>Mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males, n (%)</td>
<td>42 (57.5)</td>
<td>51 (37.8)</td>
<td>χ²(1)=7.48; p=0.006</td>
</tr>
<tr>
<td>Birth weight (BW), g</td>
<td>828.1 (174.3)</td>
<td>919.8 (142.6)</td>
<td>-91.7 (-135.9, -47.4); p=0.0001</td>
</tr>
<tr>
<td>zBirth weight</td>
<td>-0.16 (1.11)</td>
<td>-0.48 (1.39)</td>
<td>0.32 (-0.05, 0.69); p=0.094</td>
</tr>
<tr>
<td>GA, completed weeks</td>
<td>25.7 (1.5)</td>
<td>27.2 (2.1)</td>
<td>z=-1.5 (-2.0, -0.9); p&lt;0.0001</td>
</tr>
<tr>
<td>IPPV, median days (range)</td>
<td>32 (0-82)</td>
<td>10 (0-70)</td>
<td>z=-7.151; p=&lt;0.001</td>
</tr>
<tr>
<td>Oxygen therapy, median days (range)</td>
<td>99 (41-491)</td>
<td>28 (0-106)</td>
<td>z=-11.4; p=0.001</td>
</tr>
<tr>
<td>Age at follow-up, years</td>
<td>17.8 (0.7)</td>
<td>18.0 (0.8)</td>
<td>-0.2 (-0.4, 0.05); p=0.133</td>
</tr>
<tr>
<td>zWeight at 18 year follow-up</td>
<td>-0.14 (1.40)</td>
<td>-0.09 (1.47)</td>
<td>-0.05 (-0.50, 0.41); p=0.853</td>
</tr>
<tr>
<td>zHeight at 18 year follow-up</td>
<td>-0.51 (1.25)</td>
<td>-0.71 (1.04)</td>
<td>0.20 (-0.13, 0.53); p=0.235</td>
</tr>
<tr>
<td>BMI, m²/kg</td>
<td>22.6 (4.4)</td>
<td>23.4 (5.4)</td>
<td>-0.8 (-2.2, 0.7); p=0.278</td>
</tr>
<tr>
<td>zBMI at 18 year follow-up</td>
<td>0.20 (1.25)</td>
<td>0.33 (1.39)</td>
<td>-0.13 (-0.55, 0.30); p=0.560</td>
</tr>
<tr>
<td>Current asthma, n (%)*</td>
<td>13 (30.2)</td>
<td>21 (28.8)</td>
<td>χ²(1)=0.028; p=0.867</td>
</tr>
<tr>
<td>Current smokers, n (%)†</td>
<td>5 (10.9)</td>
<td>11 (14.9)</td>
<td>χ²(1)=0.392; p=0.531</td>
</tr>
</tbody>
</table>

Variables are expressed as mean (SD), unless otherwise stated; *self-reported asthma & Doctor diagnosed asthma & asthma medications; †cigarette smoking exposure

There were no significant differences in age, weight, height and BMI z-score or asthma and smoking status between the EP/ELBW with and without BPD (Table 18). Within the EP/ELBW group 5% (4/73) of those who had BPD and 18% (24/135) were small for gestational age.
8.2.2 Respiratory function tests

Spirometry was successfully measured on 100% (73/73) BPD subjects and 100% (135/135) of No-BPD subjects. Lung volume data were available for 95% (67/73) of BPD subjects and for 99% (133/135) of the controls. Six lung volume results were excluded from the BPD group and 2 from the controls, as they did not meet ATS/ERS standards. Diffusing capacity data were available for 95% (69/73) subjects and 99% (133/135) controls. Four DLCO results from the BPD group and 2 from the controls were excluded, as they did not reach ATS/ERS standards. MBNW data were available for 32% (28/73) of BPD subjects and for 39% (57/135) of No-BPD subjects. Five BPD subjects and 5 No-BPD had their MBNW data excluded as they did not reach published standards, a further 45 EP/ELBW and 76 No-BPD subjects were not able to complete MBNW tests due to equipment failure, or unavailability.

8.2.2.1 Airflow

All spirometry variables, zFEV1, zFEV1/FVC, zFEF25-75% (Table 19 and Figure 30) were significantly reduced in the BPD group compared with the No-BPD group. Bronchodilator response, specific airways effective airways resistance and specific total airways resistance (Table 19 and Figure 31) were all significantly elevated in the BPD group compared with the No-BPD group. Gender, age, height and weight were included in the model for $sR_{\text{eff}}$ and $sR_{\text{tot}}$, none were significant contributors to the model.

Table 19: BPD adjusted regression coefficients in the EP/ELBW group - Airflow

<table>
<thead>
<tr>
<th>Variable</th>
<th>Explanatory variable</th>
<th>Coefficient</th>
<th>S.E.</th>
<th>95% CI</th>
<th>p-value</th>
<th>$R^2$ Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>zFEV1</td>
<td>BPD</td>
<td>-0.730</td>
<td>0.161</td>
<td>-1.049, -0.412</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>zFEV1/FVC</td>
<td>BPD</td>
<td>-0.442</td>
<td>0.167</td>
<td>-0.771, -0.113</td>
<td>p=0.009</td>
<td></td>
</tr>
<tr>
<td>zFEF25-75%</td>
<td>BPD</td>
<td>-0.685</td>
<td>0.171</td>
<td>-1.022, -0.348</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>BDR, mL*</td>
<td>BPD</td>
<td>10.12</td>
<td>3.02</td>
<td>4.17, 16.07</td>
<td>p=0.001</td>
<td></td>
</tr>
<tr>
<td>$sR_{\text{eff}}$, kPa.s$^{-1}$</td>
<td>BPD</td>
<td>0.192</td>
<td>0.056</td>
<td>0.080, 0.303</td>
<td>p=0.001</td>
<td>8.0%</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td>0.009</td>
<td>0.037</td>
<td>-0.064, 0.081</td>
<td>p=0.809</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>0.097</td>
<td>0.071</td>
<td>-0.042, 0.237</td>
<td>p=0.171</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td></td>
<td>0.001</td>
<td>0.004</td>
<td>-0.006, 0.009</td>
<td>p=0.742</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td>0.0006</td>
<td>0.002</td>
<td>-0.003, 0.005</td>
<td>p=0.777</td>
<td></td>
</tr>
<tr>
<td>$sR_{\text{tot}}$, kPa.s$^{-1}$</td>
<td>BPD</td>
<td>0.197</td>
<td>0.061</td>
<td>0.077, 0.317</td>
<td>p=0.001</td>
<td>7.1%</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td>0.013</td>
<td>0.039</td>
<td>-0.065, 0.091</td>
<td>p=0.742</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>0.107</td>
<td>0.076</td>
<td>-0.043, 0.257</td>
<td>p=0.163</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td></td>
<td>0.0007</td>
<td>0.004</td>
<td>-0.008, 0.009</td>
<td>p=0.877</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td>0.0008</td>
<td>0.002</td>
<td>-0.003, 0.005</td>
<td>p=0.704</td>
<td></td>
</tr>
</tbody>
</table>

*change in FEV1 post bronchodilator
Figure 30: Distributional dot plots of \( z\text{FEV}_{1} \), \( z\text{FEV}_{1}/\text{FVC} \) and \( z\text{FEF}_{25-75\%} \) at the 18-year follow-up in the EP/ELBW groups comparing the group who had BPD to those who did not have BPD as neonates. \(- - -\) represents ±1.96 SDs from the mean (limits of normal); \(-\cdots\cdots\) represents mean z-score for the group.
Figure 31: Distributional dot plots of bronchodilator response (FEV₁ mL), effective airways resistance (sR<sub>eff</sub>) and total airways resistance (sR<sub>tot</sub>) actual values at the 18 year follow-up in the EP/ELBW groups comparing the group who had BPD to those who did not have BPD as neonates. --- represents the upper limit of normal for sR<sub>eff</sub> and sR<sub>tot</sub> (1.30kPa.s⁻¹). ---- represents mean value for the group.

Salbutamol 400mcg via metered dose inhaler and volumetric spacer

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Mean (mL)</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>No BPD</td>
<td>71</td>
<td>25.8</td>
<td>19.8</td>
</tr>
<tr>
<td>BPD</td>
<td>132</td>
<td>15.6</td>
<td>20.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Mean (kPa.s⁻¹)</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>No BPD</td>
<td>66</td>
<td>1.55</td>
<td>0.44</td>
</tr>
<tr>
<td>BPD</td>
<td>113</td>
<td>1.33</td>
<td>0.32</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Mean (kPa.s⁻¹)</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>No BPD</td>
<td>66</td>
<td>1.70</td>
<td>0.49</td>
</tr>
<tr>
<td>BPD</td>
<td>113</td>
<td>1.47</td>
<td>0.34</td>
</tr>
</tbody>
</table>
8.2.2.2 Lung volumes

The zFVC and zVa (Table 20 and Figure 32) was significantly reduced and zRV was elevated in the BPD group compared with those EP/ELBW subjects who did not have BPD. TLC was not significantly different between the groups.

Table 20: BPD adjusted regression coefficients in the EP/ELBW group—Lung volumes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Explanatory variable</th>
<th>Coefficient</th>
<th>S.E.</th>
<th>95% CI</th>
<th>p-value</th>
<th>R² Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>zFVC</td>
<td>BPD</td>
<td>-0.340</td>
<td>0.164</td>
<td>-0.664, -0.015</td>
<td>p=0.040</td>
<td></td>
</tr>
<tr>
<td>zVa</td>
<td>BPD</td>
<td>-0.357</td>
<td>0.133</td>
<td>-0.620, -0.095</td>
<td>p=0.008</td>
<td></td>
</tr>
<tr>
<td>TLC, L</td>
<td>BPD</td>
<td>0.007</td>
<td>0.095</td>
<td>-0.182, 0.195</td>
<td>p=0.944</td>
<td>74.6%</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td>0.109</td>
<td>0.062</td>
<td>-0.013, 0.230</td>
<td>p=0.080</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>0.782</td>
<td>0.121</td>
<td>0.543, 1.020</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td></td>
<td>0.075</td>
<td>0.007</td>
<td>0.062, 0.088</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td>-0.002</td>
<td>0.003</td>
<td>-0.009, 0.004</td>
<td>p=0.486</td>
<td></td>
</tr>
<tr>
<td>zRV</td>
<td>BPD</td>
<td>0.178</td>
<td>0.078</td>
<td>0.023, 0.332</td>
<td>p=0.024</td>
<td></td>
</tr>
</tbody>
</table>
Figure 32: Distributional dot plots of zFVC, zTLC, zRV and zVa calculated at the 18 year follow-up in the EP/ELBW groups comparing the group who had BPD to those who did not have BPD as neonates. - - - represents ±1.96 SDs from the mean (limits of normal); ----- represents mean z-score for the group.

For FVC:
- No BPD: N=73, Mean=-0.58, SD=1.24
- BPD: N=135, Mean=-0.24, SD=1.07
- p=0.040

For TLC:
- No BPD: N=69, Mean=1.21, SD=1.65
- BPD: N=133, Mean=1.09, SD=1.58
- p=0.024

For RV:
- No BPD: N=69, Mean=1.01, SD=0.49
- BPD: N=133, Mean=0.84, SD=0.55
- p=0.008

For VA:
- No BPD: N=69, Mean=-0.44, SD=1.07
- BPD: N=133, Mean=-0.08, SD=0.79
- p=0.008
8.2.2.3 Diffusing capacity

The diffusing capacity of the lung (z\(\text{DLCO}\), Table 21 and Figure 33) was significantly reduced in the BPD group compared with those who did not have BPD. This relationship was not significant after z\(\text{DLCO}\) was adjusted for alveolar volume (z\(\text{DLCO/Va}\), Table 20 and Figure 33).

Table 21: BPD adjusted regression coefficients in the EP/ELBW group – Diffusing capacity

<table>
<thead>
<tr>
<th>Variable</th>
<th>Explanatory variable</th>
<th>Coefficient</th>
<th>S.E.</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>z(\text{DLCO})</td>
<td>BPD</td>
<td>-0.521</td>
<td>0.131</td>
<td>-0.779, -0.262</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>z(\text{DLCO/Va})</td>
<td>BPD</td>
<td>-0.205</td>
<td>0.120</td>
<td>-0.442, 0.032</td>
<td>p=0.090</td>
</tr>
</tbody>
</table>

Figure 33: Distributional dot plot of z-score of \(\text{DLCO}\) and \(\text{DLCO/Va}\) at the 18 year follow-up in the EP/ELBW groups comparing the group who had BPD to those who did not have BPD as neonates. - - - represents ±1.96 SDs from the mean (limits of normal) ... represents the mean value from the reference set; --- represents mean z-score for the group.
### 8.2.2.4 Ventilatory efficiency

Ventilation efficiency within the lungs, \( z_{LCI} \) was similar in the BPD and No-BPD groups. There were no significant differences in ventilation efficiency within the acinar zone (Sacin) or the conducting zone of the lungs (Scond). Table 22 and Figure 34 display the results for ventilation efficiency.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Explanatory variable</th>
<th>Coefficient</th>
<th>S.E.</th>
<th>95% CI</th>
<th>p-value</th>
<th>( R^2 ) Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>( z_{LCI} )</td>
<td>BPD</td>
<td>0.406</td>
<td>0.510</td>
<td>-0.611, 1.423</td>
<td>p=0.429</td>
<td></td>
</tr>
<tr>
<td>( \text{Sacin, L}^{-1} )</td>
<td>BPD</td>
<td>0.002</td>
<td>0.036</td>
<td>-0.070, 0.074</td>
<td>p=0.952</td>
<td>-0.8%</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td>0.009</td>
<td>0.028</td>
<td>-0.048, 0.066</td>
<td>p=0.750</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>0.073</td>
<td>0.042</td>
<td>-0.011, 0.157</td>
<td>p=0.087</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td></td>
<td>-0.001</td>
<td>0.002</td>
<td>-0.005, 0.003</td>
<td>p=0.631</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td>-0.001</td>
<td>0.002</td>
<td>-0.004, 0.001</td>
<td>p=0.339</td>
<td></td>
</tr>
<tr>
<td>( \text{Scond, L}^{-1} )</td>
<td>BPD</td>
<td>0.012</td>
<td>0.008</td>
<td>-0.004, 0.027</td>
<td>p=0.132</td>
<td>1.7%</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td>0.008</td>
<td>0.006</td>
<td>-0.004, 0.021</td>
<td>p=0.173</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>0.007</td>
<td>0.009</td>
<td>-0.011, 0.025</td>
<td>p=0.431</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td></td>
<td>0.0002</td>
<td>0.0005</td>
<td>-0.0007, 0.001</td>
<td>p=0.606</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td>-0.0003</td>
<td>0.0003</td>
<td>-0.0008, 0.0003</td>
<td>p=0.287</td>
<td></td>
</tr>
</tbody>
</table>
Figure 34: Distributional dot plot of zLCI, Sacin and Scond at the 18 year follow-up in the EP/ELBW groups comparing the group who had BPD to those who did not have BPD as neonates. -- - - represents ±1.96 SDs from the mean (limits of normal) ... represents the mean value from the reference set; - - - represents mean value for the group.

For zLCI:
- No BPD: N=23, Mean=0.61, SD=2.17
- BPD: N=52, Mean=0.21, SD=1.98

For Sacin (L⁻¹):
- No BPD: N=22, Mean=0.186, SD=0.104
- BPD: N=52, Mean=0.162, SD=0.140

For Scond (L⁻¹):
- No BPD: N=23, Mean=0.042, SD=0.033
- BPD: N=52, Mean=0.029, SD=0.026
8.2.3 Cardiopulmonary exercise

Cardiopulmonary exercise was measured on 81% (59/73) of BPD subjects and 86% (116/135) No-BPD subjects. Thirteen BPD and 20 No-BPD sets of cardiopulmonary data were excluded from the analysis as they did not reach >1.05 for respiratory exchange ratio or >90% of their predicted HRmax.

8.2.3.1 Metabolic rate

BPD was a significant contributor to the maximal work rate achieved (Table 23 and Figure 35), where having BPD reduced the work rate maximum by over 260 Watts. Also, as expected, gender (by approximately 300 Watts higher for males), height (by approximately 8 Watts per cm increasing height) and weight (by approximately 8 Watts per kg increasing weight) all had positive influences within the model. Age did not significantly influence the model.

The V'\text{O}_2/\text{Work} relationship (Table 23 and Figure 35) was increased in the BPD subjects compared with No-BPD subjects, i.e. the amount of oxygen consumption per given work rate was slightly increased in BPD, by 0.8 mL.min.W^{-1}. As expected, V'\text{O}_2/\text{Work} at maximal exercise decreased with increasing weight, by approximately 0.02 mL.min.W^{-1} per kg increase in weight, i.e. the more weight that requires moving at maximal exercise the higher the oxygen consumption. Gender, age and height did not significantly contribute to the model.

| Table 23: Cardiopulmonary exercise BPD adjusted regression coefficients in the EP/ELBW group |
|---|---|---|---|---|---|
| Cardiopulmonary variable | Explanatory variable | Coefficient | S.E. | 95% CI | p-value |
| Workmax, W | BPD | -260.6 | 58.9 | -377.1, -144.0 | p<0.001 |
| | Age (years) | 1.7 | 37.4 | -72.3, 75.7 | p=0.964 |
| | Male | 292.3 | 75.7 | 142.6, 441.9 | p<0.001 |
| | Height (cm) | 8.3 | 4.3 | -0.2, 16.9 | p=0.057 |
| V'\text{O}_2/\text{Work}, \text{mL.min.W}^{-1} | Weight (kg) | 8.3 | 2.1 | 4.2, 12.5 | p<0.001 |
| | BPD | 0.799 | 0.248 | 0.308, 1.291 | p=0.002 |
| | Age (years) | -0.101 | 0.159 | -0.415, 0.214 | p=0.528 |
| | Male | 0.019 | 0.315 | -0.604, 0.642 | p=0.952 |
| | Height (cm) | -0.008 | 0.018 | -0.044, 0.027 | p=0.653 |
| | Weight (kg) | -0.019 | 0.009 | -0.036, -0.001 | p=0.033 |
| | R² Adjusted | 44.1% | 9.1% |
8.2.3.2 Cardiovascular function

BPD subjects had reduced maximal heart rate, by approximately 4 beats in those who had BPD (Table 24 and Figure 36). As expected, maximal heart rate achieved decreased with increasing age (by approximately 2 beats per year of age). Gender, height and did not contribute to the model.

BPD subjects had a reduced O₂ pulse (Table 24 and Figure 36) at maximal exercise compared with No-BPD participants, by approximately 1mL·beat⁻¹ for BPD subjects. Gender (by approximately 3 mL·beat⁻¹ in males) and weight (by approximately 0.1mL·beat⁻¹ per kg increasing...
weight) had small but significant associations on the maximal \(O_2\) pulse. Age and height did not significantly contribute to the model.

BPD subjects had reduced stroke volume at the ventilatory threshold (by approximately 16\(\text{mL}\) for BPD) compared with No-BPD subjects. Haemoglobin results were obtained from 37% (27/73) BPD subjects who had a mean haemoglobin of 151 \(\text{g.L}^{-1}\) (range, 127 to 174 \(\text{g.L}^{-1}\)) and 37% (50/135) No-BPD participants with a mean haemoglobin of 143 \(\text{g. L}^{-1}\) (range, 109 to 175 \(\text{g.L}^{-1}\)), therefore stroke volume at ventilatory threshold was only calculated for these subjects (Figure 36).

Table 24: Cardiopulmonary exercise BPD adjusted regression coefficients in the EP/ELBW group

<table>
<thead>
<tr>
<th>Cardiopulmonary variable</th>
<th>Explanatory variable</th>
<th>Coefficient</th>
<th>S.E.</th>
<th>95% CI</th>
<th>p-value</th>
<th>R² Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRmax, \text{beats.min}^{-1}</td>
<td>BPD</td>
<td>-3.9</td>
<td>1.7</td>
<td>-7.3, -0.5</td>
<td>p=0.025</td>
<td>4.1%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>-2.6</td>
<td>1.1</td>
<td>-4.7, -0.4</td>
<td>p=0.020</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>4.6</td>
<td>2.2</td>
<td>-2.7, 5.9</td>
<td>p=0.469</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>-0.02</td>
<td>0.1</td>
<td>-0.3, 0.2</td>
<td>p=0.872</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>0.1</td>
<td>0.06</td>
<td>-0.07, 0.2</td>
<td>p=0.374</td>
<td></td>
</tr>
<tr>
<td>(O_2)Pulse, \text{mL.beat}^{-1}</td>
<td>BPD</td>
<td>-0.982</td>
<td>0.607</td>
<td>-2.183, 0.220</td>
<td>p=0.108</td>
<td>35.7%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>0.033</td>
<td>0.388</td>
<td>-0.735, 0.801</td>
<td>p=0.932</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>2.908</td>
<td>0.768</td>
<td>1.389, 4.426</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>-0.014</td>
<td>0.044</td>
<td>-0.100, 0.072</td>
<td>p=0.750</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>0.119</td>
<td>0.022</td>
<td>0.076, 0.161</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>SV at AT, \text{mL}</td>
<td>BPD</td>
<td>-15.76</td>
<td>7.06</td>
<td>-29.94, -1.57</td>
<td>p=0.030</td>
<td>32.7%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>3.48</td>
<td>4.24</td>
<td>-5.04, 11.99</td>
<td>p=0.416</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>-6.19</td>
<td>8.83</td>
<td>-23.94, 11.56</td>
<td>p=0.487</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>1.22</td>
<td>0.43</td>
<td>0.35, 2.09</td>
<td>p=0.007</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>0.66</td>
<td>0.21</td>
<td>0.23, 1.08</td>
<td>p=0.003</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin, \text{g.L}^{-1}</td>
<td>BPD</td>
<td>-0.05</td>
<td>0.24</td>
<td>-4.8, 4.7</td>
<td>p=0.983</td>
<td>66.2%</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>26.6</td>
<td>0.23</td>
<td>22.0, 31.2</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>0.5</td>
<td>0.15</td>
<td>-2.4, 3.4</td>
<td>p=0.741</td>
<td></td>
</tr>
</tbody>
</table>
Figure 36: Distributional dot plots of maximal heart rate, maximal oxygen pulse and stroke volume at the ventilatory threshold actual values at the 18 year follow-up in the EP/ELBW groups comparing the group who had BPD to those who did not have BPD as neonates. Bars represent mean value for the group.

- **Heart rate (beats.min⁻¹)**
  - No BPD: N=63, Mean=192, SD=12
  - BPD: N=114, Mean=194, SD=12

- **O₂ pulse (mL.beat⁻¹)**
  - No BPD: N=59, Mean=12.8, SD=4.1
  - BPD: N=112, Mean=12.7, SD=4.3

- **Stroke volume at Ventilatory threshold (mL)**
  - No BPD: N=23, Mean=115.1, SD=48.5
  - BPD: N=48, Mean=119.2, SD=47.9

*p = 0.03*
8.2.3.3 Ventilatory function

Maximal ventilation (Table 25 and Figure 37) was significantly higher in males, which could reflect larger lung volumes in males. There was no association between gender, height, weight, age or BPD status and maximal ventilation.

As expected, breathing frequency (Table 25 and Figure 37) or respiratory rate decreased with increasing height (by approximately 0.5 breaths.min⁻¹ per cm increasing height) and male gender (by approximately 7 breaths.min⁻¹), which could reflect increasing lung volume with height. There was no association between weight, age or BPD and maximal breathing frequency.

The major determinants of Vtmax (Table 25 and Figure 37) were height (by approximately 30 mL per cm increasing height), weight (by approximately 6 mL per kg increasing weight) and gender (by approximately 100 mL for males). This could reflect increasing lung volume with growth in the age groups involved in this study and increased lung volumes in males. There was no association between age or BPD and maximal tidal volume achieved.

Maximal inspiratory duty cycle (Ti/Ttot, Table 25 and Figure 37) was significantly associated with age, where each year increased age was associated with an increased Ti/Ttot ratio of approximately 0.5, i.e. decreasing inspiratory time as a component of total tidal volume, or the portion of respiration when the inspiratory muscles are active and will show an alterations in ventilatory timing. There was no association between BPD, gender, height or weight and Ti/Ttot in the model.

BPD subjects used a higher percentage of their ventilatory reserve (V'E/MVV, Table 25 and Figure 37), by approximately 5% in the BPD group compared with No-BPD participants, which could reflect abnormal static lung function variables, such as reduced zFEV₁ and elevated zRV. Male subjects used a higher percentage of their V'E/MVV, by approximately 9% compared with females, this may relate to the higher maximal V'E rate and V'O₂max achieved (Table 25). Height was a small but significant contributor to the model, by approximately -0.6% per cm increase in height. Neither age nor weight contributed to the model.
Table 25: Cardiopulmonary exercise BPD adjusted regression coefficients in the EP/ELBW group

<table>
<thead>
<tr>
<th>Cardiopulmonary variable</th>
<th>Explanatory variable</th>
<th>Coefficient</th>
<th>S.E.</th>
<th>95% CI</th>
<th>p-value</th>
<th>R² Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>V’Emax, L.min⁻¹</td>
<td>BPD</td>
<td>-1.415</td>
<td>3.002</td>
<td>-7.352, 4.522</td>
<td>p=0.638</td>
<td>40.7%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>1.398</td>
<td>1.922</td>
<td>-2.404, 5.200</td>
<td>p=0.468</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>17.523</td>
<td>3.867</td>
<td>9.874, 25.171</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>0.433</td>
<td>0.221</td>
<td>-0.004, 0.870</td>
<td>p=0.052</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>0.284</td>
<td>0.106</td>
<td>0.073, 0.494</td>
<td>p=0.009</td>
<td></td>
</tr>
<tr>
<td>BFmax, breaths.min⁻¹</td>
<td>BPD</td>
<td>1.089</td>
<td>1.705</td>
<td>-2.282, 4.461</td>
<td>p=0.524</td>
<td>8.4%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>-0.334</td>
<td>1.092</td>
<td>-2.493, 1.825</td>
<td>p=0.760</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>6.990</td>
<td>2.200</td>
<td>2.646, 11.333</td>
<td>p=0.002</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>-0.500</td>
<td>0.125</td>
<td>-0.748, 0.252</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>0.041</td>
<td>0.060</td>
<td>-0.078, 0.161</td>
<td>p=0.495</td>
<td></td>
</tr>
<tr>
<td>Vtmax, L</td>
<td>BPD</td>
<td>-0.043</td>
<td>0.063</td>
<td>-0.168, 0.082</td>
<td>p=0.500</td>
<td>49.1%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>0.040</td>
<td>0.041</td>
<td>-0.040, 0.121</td>
<td>p=0.327</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>0.097</td>
<td>0.081</td>
<td>-0.063, 0.257</td>
<td>p=0.234</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>0.028</td>
<td>0.005</td>
<td>0.019, 0.037</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>0.006</td>
<td>0.002</td>
<td>0.001, 0.010</td>
<td>p=0.013</td>
<td></td>
</tr>
<tr>
<td>Ti/Ttot</td>
<td>BPD</td>
<td>-0.232</td>
<td>0.512</td>
<td>-1.245, 0.781</td>
<td>p=0.651</td>
<td>-0.2%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>0.552</td>
<td>0.392</td>
<td>-0.099, 1.203</td>
<td>p=0.096</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>-0.433</td>
<td>0.656</td>
<td>-1.730, 0.864</td>
<td>p=0.510</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>-0.014</td>
<td>0.037</td>
<td>-0.088, 0.060</td>
<td>p=0.711</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>0.003</td>
<td>0.018</td>
<td>-0.033, 0.039</td>
<td>p=0.863</td>
<td></td>
</tr>
<tr>
<td>V’E/MVV, %</td>
<td>BPD</td>
<td>4.705</td>
<td>2.588</td>
<td>-0.414, 9.825</td>
<td>p=0.071</td>
<td>7.3%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>0.957</td>
<td>1.658</td>
<td>-2.322, 4.235</td>
<td>p=0.565</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>9.370</td>
<td>3.334</td>
<td>2.775, 15.966</td>
<td>p=0.006</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>-0.618</td>
<td>0.190</td>
<td>-0.994, -0.241</td>
<td>p=0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>0.103</td>
<td>0.092</td>
<td>-0.078, 0.284</td>
<td>p=0.263</td>
<td></td>
</tr>
</tbody>
</table>
Figure 37: Distributional dot plots of maximal ventilation rate, maximal breathing frequency, maximal tidal volume, maximal inspiratory duty cycle (Ti/Ttot) and plot ventilatory reserve (V’E/MVV) actual values at the 18-year follow-up in the EP/ELBW groups comparing the group who had BPD to those who did not have BPD as neonates. ___ represents mean value for the group.
### 8.2.3.4 Gas exchange

The $\dot{V}O_2\text{max}$ (Table 26 and Figure 38) was significantly reduced in the BPD group compared with controls, by approximately 145 mL.min$^{-1}$ for BPD subjects. As expected, $\dot{V}O_2\text{max}$ increased with increasing height (by approximately 15 mL.min$^{-1}$ per cm increasing height), and increasing weight (by approximately 14 mL.min$^{-1}$ per kg increasing weight) and was also higher in males, by approximately 560 mL.min$^{-1}$. Age did not contribute to the model. When $\dot{V}O_2\text{max}$ is adjusted for body weight (mL.min.kg$^{-1}$, Table 26 and Figure 38) it was significantly reduced in BPD subjects compared with No-BPD subjects. $\dot{V}O_2\text{max}$ adjusted for body weight slightly increased with increasing height (by approximately 0.2 mL.min.kg$^{-1}$ per cm increasing height), it decreased slightly with increasing weight (by approximately 0.3 mL.min.kg$^{-1}$ per cm increasing weight) and was also higher in males, by approximately 9 mL.min.kg$^{-1}$. Age did not contribute to the model.

The $\dot{V}CO_2\text{max}$ (Table 26 and Figure 38) was significantly reduced in the BPD group compared with No-BPD participants, by approximately 160 mL.min$^{-2}$ for BPD subjects. As expected, $\dot{V}CO_2\text{max}$ increased with increasing height (by approximately 19 mL.min$^{-1}$ per cm increasing height), and increasing weight (by approximately 19 mL.min$^{-1}$ per kg increasing weight) and was also higher in males, by approximately 640 mL.min$^{-1}$. Age did not contribute to the model.

The determinant of ventilatory equivalent for O$_2$ and CO$_2$ (Figure 38) in the models (Table 26) is weight, with both $V'E/V'O_2$ and $V'E/V'O_2$ increasing by approximately 0.1 unit per kg increase in weight, this may reflect the influence of weight in peak ventilation, suggesting higher ventilation rates at peak exercise in heavier subjects. BPD status, gender, age and height did not significantly contribute to the model.

None of the factors included in the model for maximal oxygen saturation (SpO$_2$, Table 26 and Figure 38) showed any significant contributions; hence the adjusted $R^2$ for this model was -0.08%.

Male gender and weight were significantly associated with small but significant increase in the fraction expired CO$_2$ (FETCO$_2$, Table 26) level at peak exercise; this may relate to the influence of gender on $V'CO_2$. 
Table 26: Cardiopulmonary exercise BPD adjusted regression coefficients in the EP/ELBW group

<table>
<thead>
<tr>
<th>Cardiopulmonary variable</th>
<th>Explanatory variable</th>
<th>Coefficient</th>
<th>S.E.</th>
<th>95% CI</th>
<th>p-value</th>
<th>R² Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>V'O₂ max, mL.min⁻¹</td>
<td>BPD</td>
<td>-145.2</td>
<td>74.8</td>
<td>-293.1, 2.7</td>
<td>p=0.054</td>
<td>61.0%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>-29.1</td>
<td>47.9</td>
<td>-123.8, 65.6</td>
<td>p=0.544</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>559.4</td>
<td>94.8</td>
<td>371.9, 746.9</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>15.1</td>
<td>5.4</td>
<td>4.4, 25.7</td>
<td>p=0.006</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>14.4</td>
<td>2.6</td>
<td>9.2, 19.5</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>V'O₂ max, mL.min.kg⁻¹</td>
<td>BPD</td>
<td>-3.31</td>
<td>1.12</td>
<td>-5.54, -1.10</td>
<td>p=0.004</td>
<td>47.3%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>-0.52</td>
<td>0.72</td>
<td>-1.95, 0.90</td>
<td>p=0.469</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>8.73</td>
<td>1.42</td>
<td>5.91, 11.55</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>0.20</td>
<td>0.08</td>
<td>0.04, 0.36</td>
<td>p=0.015</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>-0.30</td>
<td>0.04</td>
<td>-0.37, -0.22</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>V'CO₂, mL.min⁻¹</td>
<td>BPD</td>
<td>-162.7</td>
<td>94.9</td>
<td>-350.4, 25.0</td>
<td>p=0.089</td>
<td>58.9%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>37.5</td>
<td>60.7</td>
<td>-82.6, 157.6</td>
<td>p=0.538</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>635.9</td>
<td>121.0</td>
<td>396.6, 875.1</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>18.5</td>
<td>6.9</td>
<td>4.8, 32.1</td>
<td>p=0.008</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>19.2</td>
<td>3.3</td>
<td>12.6, 25.8</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>V'O₂/V'E</td>
<td>BPD</td>
<td>-1.59</td>
<td>0.80</td>
<td>-3.17, 0.0009</td>
<td>p=0.050</td>
<td>9.6%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>-0.80</td>
<td>0.51</td>
<td>-1.82, 0.22</td>
<td>p=0.121</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>1.05</td>
<td>1.02</td>
<td>-0.96, 3.06</td>
<td>p=0.303</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>-0.01</td>
<td>0.06</td>
<td>-0.12, 0.10</td>
<td>p=0.86</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>0.08</td>
<td>0.03</td>
<td>0.03, 0.14</td>
<td>p=0.004</td>
<td></td>
</tr>
<tr>
<td>V'CO₂/V'E</td>
<td>BPD</td>
<td>-1.32</td>
<td>0.89</td>
<td>-3.07, 0.44</td>
<td>p=0.140</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>-0.09</td>
<td>0.57</td>
<td>-1.22, 1.03</td>
<td>p=0.870</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>1.09</td>
<td>1.13</td>
<td>-1.15, 3.32</td>
<td>p=0.337</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>0.03</td>
<td>0.06</td>
<td>-0.10, 0.16</td>
<td>p=0.619</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>0.11</td>
<td>0.03</td>
<td>0.05, 0.17</td>
<td>p=0.001</td>
<td></td>
</tr>
<tr>
<td>SpO₂ max, %</td>
<td>BPD</td>
<td>0.62</td>
<td>0.42</td>
<td>-0.22, 1.46</td>
<td>p=0.146</td>
<td>-0.08%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>-0.26</td>
<td>0.27</td>
<td>-0.79, 0.27</td>
<td>p=0.335</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>0.20</td>
<td>0.54</td>
<td>-0.87, 1.28</td>
<td>p=0.711</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>-0.01</td>
<td>0.03</td>
<td>-0.07, 0.05</td>
<td>p=0.718</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>-0.01</td>
<td>0.02</td>
<td>-0.04, 0.02</td>
<td>p=0.368</td>
<td></td>
</tr>
<tr>
<td>FETCO₂, kPa</td>
<td>BPD</td>
<td>-0.056</td>
<td>0.117</td>
<td>-0.288, 0.175</td>
<td>p=0.632</td>
<td>20.9%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>-0.084</td>
<td>0.075</td>
<td>-231, 0.065</td>
<td>p=0.266</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>0.262</td>
<td>0.148</td>
<td>-0.03, 0.556</td>
<td>p=0.080</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>-0.001</td>
<td>0.008</td>
<td>-0.018, 0.016</td>
<td>p=0.889</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>0.019</td>
<td>0.004</td>
<td>0.011, 0.027</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>
Figure 38: Distributional dot plots maximal oxygen consumption, maximal oxygen consumption per kg, maximal carbon dioxide production, maximal ventilatory equivalent for O₂ (V'E/V'O₂) and maximal SpO₂ actual values at the 18 year follow-up in the EP/ELBW groups comparing the group who had BPD to those who did not have BPD as neonates. ___ represents mean values for the group.
8.2.3.5 **Metabolic acidosis**

The V'O₂ achieved at the ventilatory threshold (Table 27 and Figure 39) was significantly reduced in the BPD group compared with No-BPD participants, by approximately 205 mL.min⁻¹ for BPD subjects, which may reflect deconditioning in the BPD group. As expected, V'O₂ at the ventilatory threshold increased with increasing height (by approximately 14 mL.min⁻¹ per cm increasing height), and increasing weight (by approximately 12 mL.min⁻¹ per kg increasing weight) and was also higher in males, by approximately 340 mL.min⁻¹. Age did not contribute to the model; these patterns reflect those of the V'O₂max.

Table 27: Cardiopulmonary exercise BPD adjusted regression coefficients in the EP/ELBW group

<table>
<thead>
<tr>
<th>Cardiopulmonary variable</th>
<th>Explanatory variable</th>
<th>Coefficient</th>
<th>S.E.</th>
<th>95% CI</th>
<th>p-value</th>
<th>R² Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>V'O₂ at AT, mL.min⁻¹</td>
<td>BPD</td>
<td>-205.4</td>
<td>78.8</td>
<td>-361.3, -49.4</td>
<td>0.010</td>
<td>44.5%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>-4.66</td>
<td>50.2</td>
<td>-103.9, 94.6</td>
<td>0.926</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>336.2</td>
<td>100.0</td>
<td>138.4, 534.1</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>13.7</td>
<td>5.7</td>
<td>2.4, 24.9</td>
<td>0.017</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>12.0</td>
<td>2.7</td>
<td>6.6, 17.5</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Figure 39: Distributional dot plot maximal oxygen consumption actual values at the 18 year follow-up contrasted between the groups. ___ represents mean V'O₂ at ventilatory threshold for the group.
8.2.4 Summary of results BPD compared with No-BPD within eth EP/ELBW group

There were significantly more males in the BPD group compared with the No-BPD subjects. There were no significance differences in the proportions of BPD subjects compared with the controls who reported asthma or current smoking. Five percent (4/73) of those who had BPD and 18% (24/135) were SGA, 3% of who were EP. The BPD group had reduced GA compared with the controls; there were no other substantial differences in perinatal data between those with and without BPD as a neonate.

Spirometry was successfully measured on all the EP/ELBW subjects whether they had BPD or not. Lung volumes data were available for 95% of BPD subjects and for 99% controls. Diffusing capacity data were available for 95% BPD subjects and 58% No-BPD participants. MBNW data were available for 32% BPD subjects and 39% of No-BPD participants.

All spirometry variables were significantly reduced in the BPD group compared with the controls. Specific effective airways resistance (sRs_{eff}), specific total airways resistance (sRs_{tot}) and bronchodilator response (BDR) were all significantly elevated compared with No-BPD participants.

The BPD group had slightly reduced lung volumes, as measured by zFVC and zVa; they also had the greatest elevation in residual volume, compared with No-BPD subjects.

The diffusing capacity of the lung was significantly reduced in the BPD group compared with the No-BPD participants. After adjustment with alveolar volume there was no significant difference between the groups.

There were no significant differences in the selected variables reflecting ventilation efficiency, (zLCI;SacI; Scond) when comparing the BPD group with No-BPD participants within the EP/ELBW group.

The BPD subjects had significantly reduced maximal work rate and an increased cost of this work, i.e. the amount of O$_2$ consumption per given watt of work was higher in those who had BPD as a neonate.

The BPD group had reduced stroke volume calculated at the ventilatory (anaerobic) threshold, meaning cardiac output may be reduced in the BPD group compared with control. There were no significant differences in maximal O2pulse when comparing those who had BPD and those who did not within the EP/ELBW group.

There were no differences in maximal ventilation, breathing frequency, tidal volume, inspiratory duty cycle or ventilatory reserve when comparing subjects who had BPD and those that did not in the EP/ELBW group.
The V'O_2 max was significantly reduced in the BPD group, even when adjusted for weight. V'O_2max was also reduced at the ventilatory threshold, suggestive of deconditioning, compared with control subjects. BPD subjects also had significantly reduced ventilatory equivalent for O_2 compared with the No-BPD group. There were no differences between the groups with SpO_2, ventilatory equivalent CO_2 or the fractional expired CO_2 at maximal exercise.
8.3 Effects of growth restriction in utero on respiratory function and exercise in EP survivors

8.3.1 Population characteristics of the EP survivors with respiratory function data

Perinatal characteristics of the EP group alone are shown in Table 29.

Table 28: Demographic characteristics of the EP group alone at the 18 year follow-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>EP n=181</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males, n (%)</td>
<td>85 (47.0)</td>
</tr>
<tr>
<td>Birth weight (BW), g</td>
<td>888.3 (166.6)</td>
</tr>
<tr>
<td>Birth weight z-score</td>
<td>-0.018 (0.967)</td>
</tr>
<tr>
<td>GA, completed weeks</td>
<td>26.0 (1.2)</td>
</tr>
<tr>
<td>IPPV, median days (range)</td>
<td>19 (0-82)</td>
</tr>
<tr>
<td>Oxygen therapy, median days (range)</td>
<td>56 (0-491)</td>
</tr>
<tr>
<td>Age at follow-up, years</td>
<td>17.9 (0.7)</td>
</tr>
<tr>
<td>Weight z-score at 18 year follow-up</td>
<td>-0.56 (1.12)</td>
</tr>
<tr>
<td>Height z-score at 18 year follow-up</td>
<td>-0.03 (1.45)</td>
</tr>
<tr>
<td>BMI, m²/kg</td>
<td>23.1 (5.2)</td>
</tr>
<tr>
<td>BMI z-score at 18 year follow-up</td>
<td>0.31 (1.36)</td>
</tr>
<tr>
<td>Current asthma, n (%)</td>
<td>30 (29.4)</td>
</tr>
<tr>
<td>Current smokers, n (%)</td>
<td>15 (14.2)</td>
</tr>
</tbody>
</table>

Variables are expressed as mean (SD), unless otherwise stated; *self-reported asthma & Doctor diagnosed asthma & asthma medications; †cigarette smoking exposure

8.3.2 Respiratory function tests

Spirometry was successfully measured on 100% (181/181) the EP subjects with respiratory function data. Lung volume data were available for 97% (176/181). Five lung volume results were excluded from the EP group as they did not meet ATS/ERS standards.(33,38) Diffusing capacity data were available for 97% (175/181) EP subjects. Six DLCO results from the EP group were excluded as they did not reach ATS/ERS standards.(33,46) MBNW data were available for 41% (75/181) of EP subjects. Eight EP subjects had their MBNW data excluded as they did not reach published standards, a further 106 EP subjects were not able to complete MBNW tests due to equipment failure, or unavailability.(224)

8.3.2.1 Airflow

Results for airflow variables are displayed in Table 29 and Figure 40. zFEV₁ and zFEF25-75% were positively associated with zBW. Birth weight z-score did not influence zFEV₁/FVC, bronchodilator response, or the airways resistance measures, sR_eff and sR_tot. Gender, age, height and weight were included in the model for sR_eff and sR_tot; none were significant contributors.
Table 29: zBW adjusted regression coefficients in the EP group - Airflow

<table>
<thead>
<tr>
<th>Variable</th>
<th>Explanatory variable</th>
<th>Coefficient</th>
<th>S.E.</th>
<th>95% CI</th>
<th>p-value</th>
<th>R² Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>zFEV₁</td>
<td>zBW</td>
<td>0.282</td>
<td>0.089</td>
<td>0.106, 0.459</td>
<td>p=0.002</td>
<td></td>
</tr>
<tr>
<td>zFEV₁/FVC</td>
<td>zBW</td>
<td>0.057</td>
<td>0.093</td>
<td>-0.127, 0.240</td>
<td>p=0.541</td>
<td></td>
</tr>
<tr>
<td>zFEF25-75%</td>
<td>zBW</td>
<td>0.222</td>
<td>0.096</td>
<td>0.033, 0.411</td>
<td>p=0.021</td>
<td></td>
</tr>
<tr>
<td>BDR, mL*</td>
<td>zBW</td>
<td>-0.600</td>
<td>1.699</td>
<td>-3.951, 2.757</td>
<td>p=0.726</td>
<td></td>
</tr>
<tr>
<td>sRₑff, kPa.s⁻¹</td>
<td>zBW</td>
<td>-0.028</td>
<td>0.031</td>
<td>-0.089, 0.034</td>
<td>p=0.378</td>
<td>-0.08%</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td>-0.009</td>
<td>0.042</td>
<td>-0.093, 0.075</td>
<td>p=0.833</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>0.066</td>
<td>0.081</td>
<td>-0.095, 0.227</td>
<td>p=0.417</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td></td>
<td>0.003</td>
<td>0.005</td>
<td>-0.006, 0.012</td>
<td>p=0.575</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td>0.002</td>
<td>0.002</td>
<td>-0.003, 0.006</td>
<td>p=0.488</td>
<td></td>
</tr>
<tr>
<td>sRtot, kPa.s⁻¹</td>
<td>zBW</td>
<td>-0.034</td>
<td>0.033</td>
<td>-0.100, 0.032</td>
<td>p=0.308</td>
<td>-0.2%</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td>-0.006</td>
<td>0.045</td>
<td>-0.096, 0.084</td>
<td>p=0.892</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>0.073</td>
<td>0.087</td>
<td>-0.099, 0.245</td>
<td>p=0.402</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td></td>
<td>0.002</td>
<td>0.005</td>
<td>-0.008, 0.012</td>
<td>p=0.684</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td>0.002</td>
<td>0.002</td>
<td>-0.003, 0.007</td>
<td>p=0.433</td>
<td></td>
</tr>
</tbody>
</table>

*change in FEV₁ post bronchodilator

As BPD was known to be associated with zFEV₁ and zFEF25-75%, it was important to know if the relationships with these variables and birth weight z-score were influenced by a diagnosis of BPD in the EP cohort. When BPD was added to the model for zFEV₁ and zFEF25-75%, the positive relationships between zFEV₁ and zFEF25-75% and birth weight z-score were barely affected (adjusted regression coefficients; zFEV₁ 0.266 [95% CI 0.096, 0.427]; zFEF25-75% 0.206 [95% CI 0.023, 0.390]).
Figure 40: Distributional dot plot of z-score of zFEV₁, zFEV₁/FVC and zFEF₂₅₋₇₅% at the 18 year follow-up in EP only group. - - - represents -1.96 SDs from the mean (lower limit of normal); --- represents regression line for the model; ...represents the 95% CI.
Figure 41: Distributional dot plot of bronchodilator response, $sR_{eff}$ and $sR_{tot}$ at the 18 year follow-up in EP only group. - - - represents -1.96 SDs from the mean (lower limit of normal); ...represents regression line for the model, refer to Table 29; ...represents the 95% CI.
8.3.2.2 Lung volumes

FVC z-score was positively associated with zBW (Table 30 and Figure 42). Birth weight z-score did not influence zVa, TLC or zRV. Gender, age, height and weight were included in the model for TLC, as expected gender and height were positively associated with TLC, weight and age were not significant contributors to the model for TLC (Table 30).

Table 30: zBW adjusted regression coefficients in the EP group—Lung volumes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Explanatory variable</th>
<th>Coefficient</th>
<th>S.E.</th>
<th>95% CI</th>
<th>p-value</th>
<th>R² Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC, z-score</td>
<td>zBW</td>
<td>0.228</td>
<td>0.088</td>
<td>0.055, 0.402</td>
<td>p=0.010</td>
<td></td>
</tr>
<tr>
<td>Va, z-score</td>
<td>zBW</td>
<td>0.064</td>
<td>0.074</td>
<td>-0.083, 0.211</td>
<td>p=0.391</td>
<td></td>
</tr>
<tr>
<td>TLC, L</td>
<td>zBW</td>
<td>0.101</td>
<td>0.054</td>
<td>-0.005, 0.207</td>
<td>p=0.061</td>
<td>74.2%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>0.116</td>
<td>0.070</td>
<td>-0.023, 0.255</td>
<td>p=0.101</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>0.868</td>
<td>0.135</td>
<td>0.601, 1.135</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>0.072</td>
<td>0.007</td>
<td>0.057, 0.087</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>-0.003</td>
<td>0.004</td>
<td>-0.010, 0.004</td>
<td>p=0.382</td>
<td></td>
</tr>
<tr>
<td>RV, z-score</td>
<td>zBW</td>
<td>-0.057</td>
<td>0.042</td>
<td>-0.139, 0.026</td>
<td>p=0.178</td>
<td></td>
</tr>
</tbody>
</table>
Figure 42: Distributional dot plot of zFVC, zTLC, zRV and zVa at the 18 year follow-up in EP group. --- represents -1.96 SDs from the mean (lower limit of normal); ... represents regression line for the model; ... represents the 95% CI.
8.3.2.3 Diffusing capacity

$DLCO$ z-score was positively associated with $zBW$ (Table 31 and Figure 43), even after adjusted for alveolar volume ($zDLCO/Va$).

Table 31: $zBW$ adjusted regression coefficients in the EP group – Diffusing capacity

<table>
<thead>
<tr>
<th>Variable</th>
<th>Explanatory variable</th>
<th>Coefficient</th>
<th>S.E.</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$DLCO$, $z$-score</td>
<td>$zBW$</td>
<td>0.252</td>
<td>0.071</td>
<td>0.111, 0.392</td>
<td>$p=0.001$</td>
</tr>
<tr>
<td>$DLCO/Va$, $z$-score</td>
<td>$zBW$</td>
<td>0.214</td>
<td>0.062</td>
<td>0.091, 0.337</td>
<td>$p=0.001$</td>
</tr>
</tbody>
</table>

Figure 43: Distributional dot plots of $zDLCO$ and $zDLCO/Va$ at the 18 year follow-up in EP group. --- represents -1.96 SDS from the mean (lower limit of normal); ... represents regression line for the model; ... represents the 95% CI.

As BPD was known to be associated with $zDLCO$ and $zDLCO/Va$, it was important to know if the relationships with these variables and birth weight $z$-score were influenced by a diagnosis of BPD in the EP cohort. When BPD was added to the model for $zDLCO$ and $zDLCO/Va$, the positive relationships between $zDLCO$ and $zDLCO/Va$ and birth weight $z$-score were barely affected.
(adjusted regression coefficients; zDLCO 0.242 [95% CI 0.107, 0.378]; zDLCO/Va 0.210 [95% CI 0.088, 0.332]).

### 8.3.2.4 Ventilation efficiency

Birth weight z-score did not significantly influence zLCI or ventilation efficiency within the acinar lung zone (Sacin) or within the conducting lung zones (Scond). Table 32 and Figure 44 display the results for ventilation efficiency.

Table 32: zBW adjusted regression coefficients in the EP – Ventilation efficiency

<table>
<thead>
<tr>
<th>Variable</th>
<th>Explanatory variable</th>
<th>Coefficient</th>
<th>S.E.</th>
<th>95% CI</th>
<th>p-value</th>
<th>R² Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCI, z-score</td>
<td>zBW</td>
<td>-0.472</td>
<td>0.237</td>
<td>-0.945, 0.001</td>
<td>0.051</td>
<td></td>
</tr>
<tr>
<td>Sacin, L¹</td>
<td>zBW</td>
<td>-0.021</td>
<td>0.020</td>
<td>-0.062, 0.020</td>
<td>0.300</td>
<td>-1.3%</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td>0.004</td>
<td>0.031</td>
<td>-0.058, 0.067</td>
<td>0.894</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>0.055</td>
<td>0.048</td>
<td>-0.041, 0.151</td>
<td>0.255</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td></td>
<td>-0.0005</td>
<td>0.002</td>
<td>-0.005, 0.004</td>
<td>0.833</td>
<td></td>
</tr>
<tr>
<td>Scond, L¹</td>
<td>zBW</td>
<td>-0.006</td>
<td>0.004</td>
<td>-0.015, 0.003</td>
<td>0.210</td>
<td>-3.8%</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td>0.003</td>
<td>0.007</td>
<td>-0.011, 0.016</td>
<td>0.679</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>0.003</td>
<td>0.010</td>
<td>-0.018, 0.024</td>
<td>0.781</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td></td>
<td>0.0002</td>
<td>0.0005</td>
<td>-0.0008, 0.001</td>
<td>0.711</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td>-0.00003</td>
<td>0.0003</td>
<td>-0.0006, 0.0006</td>
<td>0.916</td>
<td></td>
</tr>
</tbody>
</table>
Figure 44: Distributional dot plots of zLCl, Sacin and Scond at the 18 year follow-up in the EP group. --- represents -1.96 SDs from the mean (lower limit of normal); ... represents regression line for the model; ... represents the 95% CI.
8.3.3 Cardiopulmonary exercise

Cardiopulmonary exercise was measured on 83% (151/181) of EP subjects. Thirty EP sets of cardiopulmonary data were excluded from the analysis as they did not reach >1.05 for respiratory exchange ratio or >90% of their predicted HRmax.

8.3.3.1 Metabolic rate

As expected, gender (by approximately 300 Watts for males) and weight (by approximately 9 Watts per kg increasing weight) had positive influences within the model for maximal work rate (Table 33 and Figure 45). Age, height and zBW did not significantly influence the model.

As expected, VO₂/Work at maximal exercise decreased with increasing weight, by approximately -0.02 mL.min⁻¹.W⁻¹ per kg increase in weight, i.e. the more weight that requires moving at maximal exercise the higher the oxygen consumption (Table 33 and Figure 45). Gender, age, height and zBW did not significantly contribute to the model.

Table 33: Cardiopulmonary exercise zBW adjusted regression coefficients in the EP group

<table>
<thead>
<tr>
<th>Cardiopulmonary variable</th>
<th>Explanatory variable</th>
<th>Coefficient</th>
<th>S.E.</th>
<th>95% CI</th>
<th>p-value</th>
<th>R² Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Workmax, W</td>
<td>zBW</td>
<td>24.7</td>
<td>36.2</td>
<td>-47.1, 96.4</td>
<td>p=0.497</td>
<td>36.9%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>24.6</td>
<td>46.4</td>
<td>-67.4, 116.5</td>
<td>p=0.598</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>316.8</td>
<td>94.0</td>
<td>130.6, 503.1</td>
<td>p=0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>4.7</td>
<td>5.4</td>
<td>-6.06, 15.5</td>
<td>p=0.389</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>9.2</td>
<td>2.4</td>
<td>4.4, 14.0</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>VO₂/Work, mL.min⁻¹.W⁻¹</td>
<td>zBW</td>
<td>-0.02</td>
<td>0.2</td>
<td>-0.3, 0.3</td>
<td>p=0.895</td>
<td>2.4%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>-0.1</td>
<td>0.2</td>
<td>-0.5, 0.3</td>
<td>p=0.572</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>0.2</td>
<td>0.4</td>
<td>0.6, 0.9</td>
<td>p=0.704</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>-0.009</td>
<td>0.02</td>
<td>-0.05, 0.04</td>
<td>p=0.685</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>-0.02</td>
<td>0.01</td>
<td>-0.04, -0.001</td>
<td>p=0.038</td>
<td></td>
</tr>
</tbody>
</table>
8.3.3.2 Cardiovascular function

None of the factors included in the model for maximal heart rate (Table 34 and Figure 46) showed any significant contributions; hence the adjusted $R^2$ for this model was -1.8%.

Gender (by approximately 3 mL·beat$^{-1}$ in males) and weight (by approximately 0.1 mL·beat$^{-1}$ per kg increasing weight) had small but significant associations with the maximal $O_2$ pulse (Table 34 and Figure 46). Age, height and $z$BW did not significantly contribute to the model.

Weight had small but significant associations on the stroke volume at the ventilatory threshold (Table 34 and Figure 46), by approximately 0.65 mL per kg increasing weight. Not all the EP subjects had their haemoglobin measured due to refusal of the blood test required,
haemoglobin results were obtained from 36% (66/181) EP subjects who had a mean haemoglobin of 14.6 dl\(^{-1}\) (range, 11.4 to 17.5 dl\(^{-1}\)), therefore stroke volume at ventilatory threshold is only calculated for these subjects (Table 34). There was no significant relationship of Hb with zBW.

Table 34: Cardiopulmonary exercise zBW adjusted regression coefficients in the EP group

<table>
<thead>
<tr>
<th>Cardiopulmonary variable</th>
<th>Explanatory variable</th>
<th>Coefficient</th>
<th>S.E.</th>
<th>95% CI</th>
<th>p-value</th>
<th>R(^2) Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRmax, beats.min(^{-1})</td>
<td>zBW</td>
<td>0.05</td>
<td>1.0</td>
<td>-2.0, 2.1</td>
<td>p=0.964</td>
<td>-1.8%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>-1.9</td>
<td>1.3</td>
<td>-4.4, 0.6</td>
<td>p=0.141</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>1.3</td>
<td>2.6</td>
<td>-3.9, 6.4</td>
<td>p=0.627</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>-0.03</td>
<td>0.2</td>
<td>-0.3, 0.3</td>
<td>p=0.860</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>0.05</td>
<td>0.07</td>
<td>-0.09, 0.2</td>
<td>p=0.515</td>
<td></td>
</tr>
<tr>
<td>O(_2) Pulse, mL.beat(^{-1})</td>
<td>zBW</td>
<td>-0.103</td>
<td>0.373</td>
<td>-0.841, 0.636</td>
<td>p=0.784</td>
<td>33.9%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>0.126</td>
<td>0.468</td>
<td>-0.801, 1.052</td>
<td>p=0.789</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>3.262</td>
<td>0.919</td>
<td>1.441, 5.083</td>
<td>p=0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>-0.054</td>
<td>0.053</td>
<td>-0.160, 0.051</td>
<td>p=0.309</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>0.127</td>
<td>0.024</td>
<td>0.079, 0.176</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>SV at AT, mL</td>
<td>zBW</td>
<td>0.65</td>
<td>4.46</td>
<td>-8.35, 9.65</td>
<td>p=0.885</td>
<td>17.2%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>0.47</td>
<td>4.69</td>
<td>-9.00, 9.95</td>
<td>p=0.920</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>-7.30</td>
<td>10.85</td>
<td>-29.20, 14.60</td>
<td>p=0.505</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>0.88</td>
<td>0.57</td>
<td>-0.27, 2.02</td>
<td>p=0.129</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>0.65</td>
<td>0.25</td>
<td>0.14, 1.17</td>
<td>p=0.014</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin, g.L(^{-1})</td>
<td>zBW</td>
<td>-1.2</td>
<td>0.31</td>
<td>-7.4, 5.0</td>
<td>p=0.708</td>
<td>66.3%</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>26.5</td>
<td>0.22</td>
<td>22.1, 30.9</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>0.5</td>
<td>0.15</td>
<td>-2.4, 3.4</td>
<td>p=0.753</td>
<td></td>
</tr>
</tbody>
</table>
Figure 46: Distributional dot plots maximal heart rate, O2 pulse and stroke volume at the ventilatory threshold at the 18 year follow-up in the EP group. ... represents regression line for the model; ... represents the 95% CI.
Ventilatory function

Maximal ventilation (Table 35 and Figure 47) was significantly higher in males, which could reflect larger lung volumes in males. Weight (by approximately 0.3 L.min\(^{-1}\) per kg increasing weight) had small but significant associations with the maximal ventilation. There was no association between gender, height, age or zBW and maximal ventilation.

Breathing frequency was negatively associated with zBW (Table 35 and Figure 47), by approximately 2 breaths.min\(^{-1}\) per SD change in birth weight. As expected, breathing frequency or respiratory rate decreased with increasing height (by approximately 0.3 breaths.min\(^{-1}\) per cm increasing height), which could reflect increasing lung volume with height. There were no associations between weight, age or gender and maximal breathing frequency.

Vtmax was positively associated with zBW (Table 35 and Figure 47), by approximately 9 mL per SD increase in birth weight. The other determinants of Vtmax were height (by approximately 20 mL per cm increasing height), weight (by approximately 0.5 mL per kg increasing weight) and gender (by approximately 200 mL for males). This could reflect increasing lung volume with growth in the age groups involved in this study and increased lung volumes in males. There were no associations between age or zBW and maximal tidal volume achieved.

None of the factors included in the model for inspiratory duty cycle (Table 35 and Figure 47) showed any significant contributions; the adjusted R\(^2\) for this model was only 0.4%.

Ventilatory reserve was negatively associated with zBW (V'E/MVV, Table 35 and Figure 47), by approximately 4% per SD increase in birth weight, which could reflect abnormal static lung function variables, such as reduced zFEV\(_1\). Male subjects used a higher percentage of their V'E/MVV, by approximately 8% compared with females, this may relate to the higher maximal V'E rate and V'O\(_2\)max achieved (Table 35). Height was a small but significant contributor to the model, by approximately -0.5% per cm increase in height. Neither age nor weight contributed to the model.
Table 35: Cardiopulmonary exercise zBW adjusted regression coefficients in the EP group

<table>
<thead>
<tr>
<th>Cardiopulmonary variable</th>
<th>Explanatory variable</th>
<th>Coefficient</th>
<th>S.E.</th>
<th>95% CI</th>
<th>p-value</th>
<th>R² Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>V'Emax, L.min^1</td>
<td>zBW</td>
<td>0.446</td>
<td>1.754</td>
<td>-3.030, 3.922</td>
<td>p=0.800</td>
<td>41.5%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>0.755</td>
<td>2.254</td>
<td>-3.712, 5.220</td>
<td>p=0.738</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>20.036</td>
<td>4.523</td>
<td>11.075, 29.000</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>0.343</td>
<td>0.260</td>
<td>-0.173, 0.859</td>
<td>p=0.190</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>0.296</td>
<td>0.117</td>
<td>0.065, 0.527</td>
<td>p=0.012</td>
<td></td>
</tr>
<tr>
<td>BFmax, breaths.min^1</td>
<td>zBW</td>
<td>-2.096</td>
<td>0.933</td>
<td>-3.944, -0.249</td>
<td>p=0.027</td>
<td>8.6%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>-1.513</td>
<td>1.200</td>
<td>-3.887, 0.861</td>
<td>p=0.209</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>4.594</td>
<td>2.404</td>
<td>-0.170, 9.357</td>
<td>p=0.059</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>-0.317</td>
<td>0.138</td>
<td>-0.592, -0.043</td>
<td>p=0.024</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>0.059</td>
<td>0.062</td>
<td>-0.063, 0.182</td>
<td>p=0.341</td>
<td></td>
</tr>
<tr>
<td>Vtmax, L</td>
<td>zBW</td>
<td>0.092</td>
<td>0.035</td>
<td>0.023, 0.016</td>
<td>p=0.010</td>
<td>51.8%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>0.045</td>
<td>0.045</td>
<td>-0.044, 0.134</td>
<td>p=0.324</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>0.197</td>
<td>0.090</td>
<td>0.019, 0.374</td>
<td>p=0.030</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>0.022</td>
<td>0.005</td>
<td>0.012, 0.033</td>
<td>p=0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>0.005</td>
<td>0.002</td>
<td>0.0006, 0.010</td>
<td>p=0.026</td>
<td></td>
</tr>
<tr>
<td>Ti/Ttot</td>
<td>zBW</td>
<td>-0.219</td>
<td>0.295</td>
<td>-0.803, 0.365</td>
<td>p=0.460</td>
<td>0.4%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>0.567</td>
<td>0.383</td>
<td>-0.191, 1.329</td>
<td>p=0.141</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>-0.467</td>
<td>0.760</td>
<td>-1.972, 1.039</td>
<td>p=0.540</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>-0.029</td>
<td>0.044</td>
<td>-0.116, 0.058</td>
<td>p=0.508</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>0.006</td>
<td>0.020</td>
<td>-0.033, 0.044</td>
<td>p=0.777</td>
<td></td>
</tr>
<tr>
<td>V'E/MVV, %</td>
<td>zBW</td>
<td>-3.642</td>
<td>1.524</td>
<td>-6.662, -0.622</td>
<td>p=0.019</td>
<td>9.9%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>0.385</td>
<td>1.958</td>
<td>-3.495, 4.265</td>
<td>p=0.844</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>7.973</td>
<td>3.930</td>
<td>0.187, 15.759</td>
<td>p=0.045</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>-0.531</td>
<td>0.226</td>
<td>-0.797, -0.082</td>
<td>p=0.021</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>0.138</td>
<td>0.101</td>
<td>-0.062, 0.339</td>
<td>p=0.175</td>
<td></td>
</tr>
</tbody>
</table>
Figure 47: Distributional dot plot maximal ventilation rate, maximal breathing frequency, maximal tidal volume, maximal inspiratory duty cycle (Ti/Ttot) and ventilatory reserve (VE/MVV) at the 18 year follow-up in the EP group. ... represents regression line for the model; ... represents the 95% CI.
8.3.3.4 Gas exchange

None of the gas exchange variables (\(V'O_2\)max, \(V'O_2\)max/kg, \(V'CO_2\)max, \(V'E/V'O_2\), \(V'E/V'CO_2\), SpO2 and FETCO2) measured during exercise was related to zBW (Table).

Male sex and weight were significant determinants for \(V'O_2\)max (by approximately 647 mL.min\(^{-1}\) for males and 14.8 mL.min\(^{-1}\) per kg increasing weight; Table and Figure). Age and height did not contribute to the model.

Male sex and weight were significant determinants of \(V'O_2\)max is adjusted for body weight (by approximately 9.6 mL.min.kg\(^{-1}\) for males and -0.3 mL.min.kg\(^{-1}\) per kg increasing weight; Table 36 and Figure 48). Age and height were not significant contributors to the model.

Male sex and weight were significant determinants of \(V'CO_2\)max (by approximately 741 mL.min\(^{-1}\) for males and 19.6 mL.min\(^{-1}\) per kg increasing weight; Table 36 and Figure 48). Age and height were not significant contributors to the model.

The determinant of ventilatory equivalent for O\(_2\) and CO\(_2\) in the models (Table 36 and Figure 48) is weight, with both \(V'E/V'O_2\) increasing by approximately 0.08 units per kg increase in weight and \(V'E/V'CO_2\) increasing by approximately 1.06 units per kg increase in. Age, sex and height did not significantly contribute to the model.

Age, sex, height and weight did not significantly contribute to the model for SpO2 (Table 36 and Figure 48) or FETCO2 (Table 36 and Figure 48).
Table 36: Cardiopulmonary exercise zBW adjusted regression coefficients in the EP group

<table>
<thead>
<tr>
<th>Cardiopulmonary variable</th>
<th>Explanatory variable</th>
<th>Coefficient</th>
<th>S.E.</th>
<th>95% CI</th>
<th>p-value</th>
<th>R² Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V'O_{\text{max}, \text{mL.min}} )</td>
<td>zBW</td>
<td>46.8</td>
<td>44.4</td>
<td>-41.1, 134.7</td>
<td>0.294</td>
<td>60.3%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>-36.2</td>
<td>56.6</td>
<td>-148.3, 75.9</td>
<td>0.524</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>647.4</td>
<td>111.1</td>
<td>427.3, 867.5</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>9.3</td>
<td>6.4</td>
<td>-3.5, 22.0</td>
<td>0.152</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>14.8</td>
<td>2.9</td>
<td>9.1, 20.4</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>( V'O_{\text{max}, \text{mL.min.kg}} )</td>
<td>zBW</td>
<td>0.4</td>
<td>0.7</td>
<td>-1.0, 1.7</td>
<td>0.601</td>
<td>43.3%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>-0.6</td>
<td>0.9</td>
<td>-2.3, 1.1</td>
<td>0.505</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>9.6</td>
<td>1.7</td>
<td>6.3, 13.0</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>0.1</td>
<td>0.1</td>
<td>-0.08, 0.3</td>
<td>0.229</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>-0.3</td>
<td>0.04</td>
<td>-0.4, -0.2</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>( V'C_{\text{max}, \text{mL.min}} )</td>
<td>zBW</td>
<td>23.908</td>
<td>56.13</td>
<td>-87.32, 135.14</td>
<td>0.671</td>
<td>58.1%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>38.7</td>
<td>72.1</td>
<td>-104.2, 181.7</td>
<td>0.592</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>741.6</td>
<td>142.9</td>
<td>458.4, 1024.7</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>12.5</td>
<td>8.2</td>
<td>-3.8, 28.9</td>
<td>0.131</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>19.6</td>
<td>3.7</td>
<td>12.3, 26.9</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>( V'O/V'E )</td>
<td>zBW</td>
<td>0.62</td>
<td>0.48</td>
<td>-0.32, 1.56</td>
<td>0.196</td>
<td>6.1%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>-0.56</td>
<td>0.61</td>
<td>-1.76, 0.64</td>
<td>0.357</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>1.50</td>
<td>1.19</td>
<td>-0.86, 3.86</td>
<td>0.210</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>-0.07</td>
<td>0.07</td>
<td>-0.21, 0.06</td>
<td>0.297</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>0.08</td>
<td>0.03</td>
<td>0.02, 0.14</td>
<td>0.011</td>
<td></td>
</tr>
<tr>
<td>( V'C/V'E )</td>
<td>zBW</td>
<td>0.29</td>
<td>0.53</td>
<td>-0.76, 1.33</td>
<td>0.587</td>
<td>10.9%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>0.28</td>
<td>0.68</td>
<td>-1.07, 1.62</td>
<td>0.684</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>1.63</td>
<td>1.34</td>
<td>-1.03, 4.29</td>
<td>0.227</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>-0.02</td>
<td>0.08</td>
<td>-0.17, 0.13</td>
<td>0.808</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>1.06</td>
<td>0.03</td>
<td>0.04, 0.174</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>( SpO_{\text{max}, %} )</td>
<td>zBW</td>
<td>0.11</td>
<td>0.25</td>
<td>-0.39, 0.60</td>
<td>0.665</td>
<td>-2.3</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>-0.17</td>
<td>0.32</td>
<td>-0.80, 0.47</td>
<td>0.603</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>0.61</td>
<td>0.65</td>
<td>-0.68, 1.89</td>
<td>0.353</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>-0.03</td>
<td>0.04</td>
<td>-0.11, 0.04</td>
<td>0.388</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>-0.01</td>
<td>0.02</td>
<td>-0.05, 0.02</td>
<td>0.478</td>
<td></td>
</tr>
<tr>
<td>( FETC_{\text{O}_2}, \text{kPa} )</td>
<td>zBW</td>
<td>0.059</td>
<td>0.067</td>
<td>-0.074, 0.191</td>
<td>0.384</td>
<td>20.9%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>-0.034</td>
<td>0.085</td>
<td>-0.204, 0.135</td>
<td>0.687</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>0.325</td>
<td>0.168</td>
<td>-0.007, 0.657</td>
<td>0.055</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>-0.008</td>
<td>0.010</td>
<td>-0.027, 0.011</td>
<td>0.410</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>0.019</td>
<td>0.004</td>
<td>0.011, 0.028</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>
Figure 48: Distributional dot plots maximal $O_2$ consumption, maximal $O_2$ consumption per kg, maximal oxygen saturation, maximal $CO_2$ production, ventilatory equivalent for $O_2$ and ventilatory equivalent for $CO_2$ at the 18 year follow-up in the EP group. ... represents regression line for the model; ... represents the 95% CI.
8.3.3.5 Metabolic acidosis

The $V'O_2$ measured at the ventilatory threshold during exercise was not related to $zBW$ (Table).

Male sex and weight were significant determinants for $V'O_2$ at AT (by approximately 348 mL.min$^{-1}$ for males and 13.3 mL.min$^{-1}$ per kg increasing weight; Table 37 and Figure 49). Age and height did not contribute to the model.

Table 37: Cardiopulmonary exercise EP only adjusted regression coefficients

<table>
<thead>
<tr>
<th>Cardiopulmonary variable</th>
<th>Explanatory variable</th>
<th>Coefficient</th>
<th>S.E.</th>
<th>95% CI</th>
<th>p-value</th>
<th>R² Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V'O_2$ at AT, mL.min$^{-1}$</td>
<td>$zBW$</td>
<td>4.4</td>
<td>47.1</td>
<td>-88.9, 97.7</td>
<td>p=0.925</td>
<td>40.3%</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>7.7</td>
<td>60.7</td>
<td>-112.5, 128.0</td>
<td>p=0.899</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>348.4</td>
<td>120.0</td>
<td>110.6, 586.3</td>
<td>p=0.004</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>9.8</td>
<td>7.0</td>
<td>-4.0, 23.6</td>
<td>p=0.161</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>13.3</td>
<td>3.1</td>
<td>7.1, 19.4</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Figure 49: Distributional dot plot of maximal $O_2$ consumption at the ventilatory threshold at the 18 year follow-up in the EP group. ... represents regression line for the model; ... represents the 95% CI.
8.3.4 Summary of results effects of growth restriction in utero

Forced expiratory volume in the first second, zFEF<sub>25-75</sub>%, zFVC, DL<sub>CO</sub> and DL<sub>CO/Va</sub> were all positively associated, and zLCI negatively associated with zBW, i.e. improving zBW was associated with improvements in these lung function variables. Neither of the specific airways resistance measures, zFEV<sub>1</sub>/FVC, bronchodilator response, zVa, TLC, zRV, Sacin nor Scond were significantly influenced by zBW.

Breathing frequency and ventilatory reserve were negatively associated with zBW. Tidal volume was positively associated with zBW. None of the other cardiopulmonary exercise variables were influenced by zBW.
9 Discussion

9.1 Summary of Main Findings

This is the largest longitudinal follow-up study to report comprehensive respiratory function and cardiopulmonary exercise assessments in a geographically-selected cohort of EP/ELBW subjects born in the post-surfactant era in late adolescence/early adulthood compared with a contemporaneous NBW control group.

The EP/ELBW subjects had significant impairments in lung function variables reflecting airflow, air trapping and the diffusing capacity of their lungs, compared with controls, with the greatest deficits apparent in those EP/ELBW survivors who had BPD as a neonate. The EP/ELBW group also had significant impairments in cardiopulmonary variables reflecting the maximal oxygen consumption, oxygen consumption at the anaerobic threshold, the amount of oxygen delivered to the muscles per heartbeat, stroke volume, maximal work rate, the cost of that work rate and they used a greater amount of their ventilatory or respiratory reserve, again the greatest deficits apparent in those EP/ELBW survivors who had BPD as a neonate, with the exception of delivery of oxygen to the muscles and ventilatory changes with exercise. Within the EP only group, i.e. those subjects whose gestational age was <28 weeks’, growth restriction was associated with impairments in lung function variables reflecting airflow and the diffusing capacity of their lungs, and during exercise growth restriction was associated with altered ventilation patterns and greater use of the ventilatory reserve to achieve maximal exercise.

9.2 Relationships with Other Studies

Lung function outcomes in this cohort have previously been reported from an 8-year old follow-up and included spirometry and lung volume assessments.(186) The results are similar to those found in the current study at the 18-year follow-up, suggesting that these impairments are persistent through childhood and into late adolescence.

Respiratory outcomes for EP/ELBW survivors at similar ages to the current from the earlier pre-surfactant era have been widely reported. Those studies have mostly reported three major findings: firstly, airflow obstruction is consistent, with the greatest abnormalities seen in those survivors who had BPD as a neonate; (188,190,215,230) secondly, elevated residual volume (RV) and its ratio to total lung capacity (RV/TLC), suggesting that air trapping and/or reduced lung elasticity is evident in the EP/ELBW group, especially in those with BPD; and thirdly, despite the improvement in lung function over the teenage years some respiratory impairment persists in adults who had previously had BPD as an infant. All of the above findings from the pre-surfactant era are present in the current study, from the post-surfactant era. It must be recognised that the
surfactant used for the current cohort was one of the earlier artificial surfactants (Exosurf™), and its use was restricted to those with the most severely established lung disease. Consequently surfactant use for the current cohort may not have had the chance to reduce lung morbidity substantially, or at least sufficiently enough to improve lung function in EP/ELBW survivors at 18 years of age. As outlined in the literature review, studies of cohorts from the post-surfactant era are still finding airway obstruction and air-trapping, albeit in younger children, and results are still worse in those with the “New BPD” compared with those with no BPD.

The findings of the current study are consistent with the lung pathologies seen in EP/ELBW infants who die, including impaired alveolar and vascular growth, and subsequent lung damage from mechanical ventilation and supplemental oxygen, which lead to the development of BPD. The current study also suggests that these lung pathologies are not restricted to those who had BPD only, but extend to all EP/ELBW survivors. The current study showed all spirometry variables, especially those reflecting airflow were significantly reduced in the EP/ELBW group compared with the control group, and perhaps not surprisingly the EP/ELBW group had elevated residual volume, suggesting gas trapping or loss of elastic properties of the lungs. The EP/ELBW group also had significantly reduced lung diffusion capacities that were not explained by changes in ventilation efficiency within the lungs, when compared with controls and may relate to impaired alveolar growth following preterm birth and improper repair after the damage incurred following the development of BPD. This may suggest that gas-trapping within the EP/ELBW survivors is homogenous within their lungs and therefore would not affect the amount of ventilation heterogeneity.

Respiratory outcomes for those EP subjects who were growth restricted, i.e. those with abnormally low birth weight z-scores adjusted for gestation, were in line with published data from animal studies. These studies suggest that intrauterine growth restriction, resulting from maternal under nutrition, even in late gestation has adverse effects of airway structure, and therefore airflow, and the gas exchange ability within the lungs, with reduced alveolar surface areas and reduced pulmonary diffusion capacity. BPD in the growth restricted subjects had no further influence on the impairment seen in airflow and diffusion capacity, suggesting growth restriction in the EP subjects was the greatest influence on these lung function outcomes.

The current study has shown clear impairments on maximal oxygen consumption, work rates and alterations in ventilatory patterns in EP/ELBW subjects, especially those who had BPD as a neonate or who were growth restricted at birth. Cardiopulmonary outcomes in EP/ELBW survivors in late adolescence in the pre-surfactant era have not been widely reported, and those who have report inconsistent findings. The published studies have differing cardiopulmonary exercise protocols, some of which may be inappropriate to use when testing children and adolescents, use differing exercise devices, e.g. treadmill or cycle or free running, small sample sizes and differing
definitions of BPD. All these differences make comparison of the current study with the literature difficult. The small samples sizes also mean many of the studies are inadequately powered to detect differences that may be clinically important. There is currently one other group of researchers who have published cardiopulmonary exercise data from subjects in the post-surfactant era in a cohort of 11-year-old EP subjects. This group, Welsh et al. report similar impairments to maximal oxygen consumption, work rates achieved and similar alterations in ventilation at peak exercise as reported in the current study.

One third of the published studies show a reduction in maximal oxygen consumption (Table 5). Fifty percent of these studies demonstrated changes in ventilation indices, such as reduced tidal volume and minute ventilation. Two studies showed increased prevalence of exercise induced bronchoconstriction. Only a couple of studies have shown reductions in oxygen pulse and heart rate. From recent studies of larger cohorts of preterm infants, significant decreases in exercise capacity were reported despite normal mean lung function or mild small airway obstruction and gas trapping, which suggest that impaired exercise tolerance was perhaps secondary to poor fitness that may be improved with an exercise training program.

The EP/ELBW subjects had to use a greater proportion of their ventilatory reserve ($\uparrow V'E/MV$) to achieve maximal exercise and that and the cost of that work rate ($V'O_2/Work$) was greater may mean the EP/ELBW subjects are working harder to achieve maximal exercise levels that compared with controls. This may in part be due to the increased resistive load of breathing due to the obstructive patterns ($\downarrow zFEV_1$, $\downarrow zFEF_{25-75}$, $\downarrow zFEV_1/FVC$, $\uparrow sR_{\text{eff}}$ and $\uparrow sR_{\text{tot}}$), impaired diffusion capacity ($\downarrow DL_{CO}$ and $DL_{CO}/Va$), whether the diffusion limitation originates from the diffusive properties of the lung or the pulmonary vascular bed, and increased gas trapping or loss of elastic properties within the lungs ($\uparrow RV/TLC$) seen in baseline lung function measures and the added impairments in oxygen pulse ($\downarrow O_2\text{pulse}$) and stroke volumes ($\downarrow SV$ at AT) during cardiopulmonary exercise. The impairments in airflow and diffusion capacity appear to be driven by growth restriction amongst the EP only subjects ($\uparrow zBW$ associated with $\uparrow zFEV_1$, $\uparrow FEF_{25-75}$ and $\uparrow zDL_{CO}$). These impairments may in turn lead to reduced levels of oxygen consumption at peak exercise in the EP/ELBW subjects. In addition to this the reduced oxygen consumption EP/ELBW survivors achieved at the ventilatory or anaerobic threshold may indicate a reduced level of fitness amongst these subjects compared with controls. Having BPD as a neonate does not have further impact on the oxygen pulse or stroke volume, but does affect baseline lung function, suggesting prematurity may be more of an influence on oxygen pulse and stroke volume than BPD per se. Being growth restricted does influence ventilatory patterns, meaning they use more of their ventilatory reserve to achieve maximal exercise.
The Barker hypothesis suggests that a fetus in response to intrauterine stress, such as undernutrition or hypoxia, makes adaptations that may lead to permanent changes in organ structure and function. Barker et al. suggest that the in utero changes resulting in growth restriction may constrain airway growth and peripheral lung development predisposing these infants to longer term chronic airflow impairment. The findings of this study, and in particular of those growth restricted subjects, are in line with theory, such as $\downarrow z FEV_{1}$, $\downarrow z FEF25-75\%$ and $\downarrow z DLCO$.

9.3 Strengths of the Study

The strengths of this study are its large numbers, geographical setting in the post-surfactant era and the recruitment at birth of a contemporaneous control group. This means the results are more generalizable to other populations of EP/ELBW survivors in the post surfactant era. In addition, the results are more applicable to those EP/ELBW babies born today, until superseded by more contemporary data. The preterm subjects were selected based on birth weight and gestational age; this allowed us to look at the effect of growth restriction on lung function cardiopulmonary exercise data.

Strengths also include the masking of specialist paediatric researchers to the birth status and previous medical history of each subject until after all subjects had been assessed. Furthermore, strict quality control procedures for lung function cardiopulmonary exercise testing in accordance with published international guidelines were applied to each subject. This study also measured comprehensive lung function and cardiopulmonary exercise data on the same subjects at the same visit.

Using appropriate reference values for each of the lung function and cardiopulmonary exercise data is essential to allow valid comparisons between different population groups. If inappropriate reference data are used to interpret lung function and cardiopulmonary data important differences may be missed. This point can be illustrated in Figure 20, where total lung capacity and residual volume were higher than predicted among the control group. If I did not have the control group to compare results with I may have concluded, incorrectly, that total lung capacity in EP/ELBW survivors was significantly elevated. Currently available reference equations cover a wide age range (3-95 years), are adjusted for age, gender, height and ethnicity, and allow for direct comparison between the different sub groups. There are no all-age references for the remainder of the lung function variables, therefore in most cases the most appropriate reference equations were different for those subjects under and over 18 years of age, which appears to be the cut-off point for lung function based reference equations. For reference equations relating to cardiopulmonary exercise the situation is worse, there are few appropriate reference sets for children or adults, most are based on data collected from small populations, or only one gender.
and there is a paucity of reference data during puberty, especially relating to girls. Therefore without contemporaneous control subjects who were matched and recruited at the same time as the preterm group appropriate interpretation of the data would not be possible, and may lead to erroneous outcomes. It therefore a major strength of this study that control subjects were matched with the EP/ELBW cohort on gender, mother’s health insurance status, and country of birth, and were randomly selected from those eligible born on the date that an EP/ELBW survivor was expected to be born.

9.4 Weaknesses of the Study

The weaknesses of this study relate to incomplete follow-up of both cohorts over the study period, although those assessed were similar to those not assessed and hence we consider the results to be applicable to the whole EP/ELBW group. The subjects who attended for and were coordinated enough to perform lung function and exercise testing may underestimate the extent of impairment, as those with worse disease may also have neurosensory and/or physical disability that prevented them taking part in the assessments.

The questionnaire used to establish clinical status is not a validated questionnaire. Participants were required as part of the larger study to respond to a few dozen questionnaires. In order to reduce the number of questionnaires, several validated questionnaires were merged to form the questionnaire included in Appendix 2. In an ideal setting each area covered by the questionnaire, including physical activity, atopic status, smoking status and asthma status should be individual validated questionnaires to allow in-depth analysis of the clinical associations that may occur between these and objective data.

Smoking status was established using results from the questionnaire, rather than cotinine analysis. In a previous study from the same group of investigators on a different cohort of ex-preterm survivors in late adolescence, urinary cotinine values correlated well with a self-reported history of smoking, so it was considered that the time and expense of collecting urine samples and assaying for the current study was not justified. Measuring smoking status objectively, using cotinine levels could be important for future studies, especially given the associations seen between smoking status, preterm birth and lung function. Further lung function tests that could be added to the testing protocol to clarify the airway pathology could include (a) direct and indirect airway challenges; (b) induced sputum; (c) exhaled nitric oxide.
9.5 Clinical Relevance

Due to their extreme immaturity and/or growth restriction, the EP/ELBW survivors may have alveoli that have fewer more simplified structure, are in many cases surfactant-deficient, with disrupted development of the surrounding microvasculature. When these EP/ELBW infants develop respiratory distress and require assisted ventilation and supplemental oxygen, further damage occurs to small airways and the lung parenchyma. In addition, these infants have a compliant chest wall; which may lead to uneven distribution of mechanical ventilation and oxygen within the airways and alveoli. Well-ventilated areas may receive greater tidal volumes than atelectatic or surfactant-deficient regions, and suffer damage to conducting airways as well as the gas exchange sites within the acinar lung zone and may have led to the reduced diffusion capacity seen in the EP/ELBW group.

Abnormal lung growth and development in turn result in a reduced peak lung function as an individual reaches early adulthood. If further damage to the lungs occurs from an external insult, such as cigarette smoking, the natural decline in lung function may be accelerated. This may lead to accelerated decline and earlier presentation to adult physicians with symptoms that may mimic smoking-related disease such as chronic obstructive pulmonary disease (COPD). Given the findings of adverse lung function in EP/ELBW subjects who were smokers, they should all be advised to avoid cigarette smoke, particularly those who had BPD as infants. The current study shows the prevalence of current smoking within the EP/ELBW group is not different to the control group.

COPD and emphysema are common diseases in adult respiratory medical practice. COPD and emphysema are disease processes related to smoking, severe asthma or chronic infection, and result in destruction of alveoli. BPD develops from disruption in the development of alveoli, and may mimic the symptoms of COPD as the populations of mechanically ventilated neonates’ progress through adulthood.(111,191,192) Since the cohorts first described by Northway are now in their 50s respiratory physicians in adult medicine must increasingly be aware of perinatal history and investigate a differential diagnosis for those young adults presenting with emphysema.(111) Neonates who receive mechanical ventilation and oxygen therapy should be followed into adulthood to further classify outcomes and provide information for differential diagnoses.

Despite the concerns about the long term effects of EP/ELBW birth it is clear that the short-term outcomes of neonates have improved over time, particularly with the advent of altered ventilation strategies such as permissive hypercapnoea, antenatal corticosteroids and postnatal surfactant treatment. The magnitude of the respiratory impairment found in survivors after EP/ELBW birth can be significant but most are able to live normal lives. With improvements to existing treatment and new treatments implemented in the future, we may expect further improvements in long-term respiratory health and neurological function in the years to come.
The questions regarding whether respiratory impairments in EP/ELBW survivors are related to prematurity itself and the immature lung’s early exposure to the extrauterine environment, or related to the actual root causes of preterm delivery, not all of which are known at present, or to the medical interventions that occur after preterm birth, such as ventilator support and supplemental oxygen therapy in the neonatal unit, or a combination of all these remain uncertain as all these factors are related and teasing out the cause of each individual influence is difficult.
9.6 Conclusions and Future Directions

EP/ELBW survivors have more impairment in airflow, air-trapping, diffusion within the lung and ventilation efficiency within the lungs at 18 years of age than do normal birth weight controls. These impairments are worse in those EP/ELBW survivors who had BPD as a neonate. Perinatal factors, including lower birth weight for gestational age, have a significant influence these impairments.

If this study was to be repeated at a later date with the same cohort or at the same age with a newer EP/ELBW cohort I would suggest some changes to the protocol. I would measure spirometry, lung volumes and diffusion capacity again, as these are widely available tests and are reasonably well understood within the wider community and provide informative information regarding impairments in airflow, gas-trapping and diffusion limitation. Again, I would measure MBW, newer commercial equipment is now available and allows measurement reflecting function of the conducting airways and acinar lung zone without the complicated analysis involved in this study, MBW is also a respiratory function test that can be applied to all age groups. Sedated and unsedated infants are able to performed MBW, as are pre-schoolers, adolescents and adults with relative ease. I would include formal assessments of stroke volume and cardiac output, and ambulatory blood pressure measurements before, during and after the cardiopulmonary exercise test. Given the apparent deficit in oxygen delivery to the peripheral muscles (O2pulse) a formal assessment of this process could be included, such as near infrared spectroscopy, this would allow the distinction between perfusion and diffusion limitation in subjects with reduced V’O2max.(292) Alongside the exercise testing the addition of gait analysis or a measure of co-ordination, especially as the subjects approach maximal exercise would be useful, as described by this study there were 16 subjects (14 EP/ELBW and 2 controls) who had noticeable co-ordination issues or “wobbly legs” at the peak of exercise. Four of the EP/ELBW subjects were excluded from the analysis because this lack of co-ordination or “wobbly leg” issue meant they were not able to achieve maximal exercise. This may be an underestimate of the actual effect as these co-ordination issues, many more subjects may be affected by this albeit more subtly and have reduced V’O2max because of it. Future cohorts should make allowance for analysis of respiratory and neurological outcomes with regards corticosteroid exposure associated with mild spastic diplegia in severe cases of early lung disease, as a possible explanation of the aforementioned “wobbly legs”.(119)

In contrast to other lung function tests, excellent reference data are available for spirometry as a result of the superlative work of the Global Lungs Initiative. Results were collated from over 57,000 individuals from 72 centers in 33 countries spanning the age range from 3 to 95 years.(69) These reference data are cross-sectional in nature so still remain problematic for interpretation of longitudinal results but still provide a de facto reference population for
spirometry and will enhance interpretation of spirometry measurements at all ages and in individuals of various ethnicities in future studies.

There is a high incidence of persistent lung function abnormalities among EP children born in the 1990s, which is largely obstructive in nature and likely to have long-term implications for future lung health. Spirometry proved to be an effective means of detecting these persistent abnormalities in survivors of EP birth and BPD, although discrimination could be improved in laboratory-based assessments by including measures of specific resistance and/or ventilation inhomogeneity. It is vital that the longer-term effects of EP/ELBW on lung function are determined throughout adulthood, as it appears almost certain that many of them will develop COPD much earlier in adult life than would otherwise be expected. To minimise the risk of early onset COPD in adulthood, efforts should be made to preserve existing lung reserves by encouraging EP/ELBW children to lead a healthy lifestyle with respect to diet, exercise and avoidance of smoking. Also, measures to prevent lung injury before and after preterm delivery, long term follow-up and appropriate treatment of lung diseases in childhood and adolescence will become increasingly important.
10 References


(74) Australian Bureau of Statistics. 3304.0 - Perinatal Deaths, Australia.


(126) Nixon PA, Washburn LK, Schechter MS, O'Shea TM. Follow-up study of a randomized controlled trial of postnatal dexamethasone therapy in very low birth weight infants: effects on pulmonary outcomes at age 8 to 11 years. J Pediatr 2007 Apr;150(4):345-350.


(168) Universities of Fribourg, Lausanne and Bern (Switzerland) with the support of the Swiss Virtual Campus. Human Embryology: Online course in embryology for medicine students. 2008; Available at: http://www.embryology.ch/anglais/pcardio/patholcardio03.html. Accessed 09/24, 2014.


(286) Normal VO₂peak values for Children and Adolescents. ; April 2011.


11 Appendices

Appendix 1: Example of the individualised cardiopulmonary exercise protocol used for the current study. The example shows the protocol for a made-up male subject, whose age was 18 years of age, height 175cms and weight 75kgs.

![Department Respiratory Medicine](image)

Royal Children's Hospital
Flemington Road
Parkville, Victoria, Australia 3052

**ID:** Example  
**Height (cm):** 175

**Name:** John Doe  
**Weight (kg):** 75

**Gender:** Male  
**Scientist:** Any Info:

**DOB:** 1/01/1991  
**Any Info:**

**Date:** 18/01/1900  
**BMI:** 24

**Age:**

Baseline VO2: 250  
Male Predicted VO2 mLs/min: 4227  
Female Predicted VO2 mLs/min: 3328  
Male Wmax: 378.8  
Female Wmax: 293  
Wasserman

*Get participant to comfortable running speed*

*Need to see plateau in peak VO2*

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Load (watts)</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 min</td>
<td>Rest Values = 0</td>
<td></td>
</tr>
<tr>
<td>2 min</td>
<td>Rest Values = 0</td>
<td></td>
</tr>
<tr>
<td>3 min</td>
<td>Alter Load = 75</td>
<td></td>
</tr>
<tr>
<td>4 min</td>
<td>Alter Load = 75</td>
<td></td>
</tr>
<tr>
<td>5 min</td>
<td>Alter Load = 114</td>
<td></td>
</tr>
<tr>
<td>6 min</td>
<td>Alter Load = 152</td>
<td></td>
</tr>
<tr>
<td>7 min</td>
<td>Alter Load = 189</td>
<td></td>
</tr>
<tr>
<td>8 min</td>
<td>Alter Load = 227</td>
<td></td>
</tr>
<tr>
<td>9 min</td>
<td>Alter Load = 265</td>
<td></td>
</tr>
<tr>
<td>10 min</td>
<td>Alter Load = 303</td>
<td></td>
</tr>
<tr>
<td>11 min</td>
<td>Alter Load = 341</td>
<td></td>
</tr>
<tr>
<td>12 min</td>
<td>Alter Load = 379</td>
<td></td>
</tr>
<tr>
<td>13 min</td>
<td>Alter Load = 417</td>
<td></td>
</tr>
<tr>
<td>14 min</td>
<td>Alter Load = 455</td>
<td></td>
</tr>
<tr>
<td>15 min</td>
<td>Alter Load = 492</td>
<td></td>
</tr>
<tr>
<td>16 min</td>
<td>Alter Load = 530</td>
<td></td>
</tr>
<tr>
<td>17 min</td>
<td>Alter Load = 568</td>
<td></td>
</tr>
<tr>
<td>18 min</td>
<td>Alter Load = 606</td>
<td></td>
</tr>
<tr>
<td>19 min</td>
<td>Recovery Values = 0</td>
<td></td>
</tr>
<tr>
<td>20 min</td>
<td>Recovery Values = 0</td>
<td></td>
</tr>
</tbody>
</table>
Appendix 2: Respiratory questionnaire used for the current study.

**Respiratory Questionnaire**

*Study ID ____________________________  Today’s Date_________________________

THIS IS AN ANONYMOUS QUESTIONNAIRE

*Please write a number in the box below, if you don’t exercise please write 0.

Think only about those physical activities done for at least 10 minutes at a time.

1. During the last 7 days, on how many days did you walk at a brisk pace - a brisk pace is a pace at which you are breathing harder than normal? [ ] Days per week [ ] Hours per day

2. During the last 7 days, on how many days did you do moderate physical activities? ‘Moderate’ activities make you breathe harder than normal, but only a little? [ ] Days per week [ ] Hours per day

3. During the last 7 days, on how many days did you do vigorous physical activities? ‘Vigorous’ activities make you breathe a lot harder than normal (‘huff and puff’)? [ ] Days per week [ ] Hours per day

4. Thinking about all your activities over the last 7 days (including brisk walking), on how many days did you engage in:
   - At least 30 minutes of moderate activity (including brisk walking) that made you breathe a little harder than normal, OR
   - At least 15 minutes of vigorous activity that made you breathe a lot harder than normal (‘huff and puff’)? [ ] Days per week

5. Describe your regular physical activity over the past six months. Regular physical activity means at least 15 minutes of vigorous activity (makes you ‘huff and puff’) or 30 minutes of moderate activity (makes you breathe slightly harder than normal) each day for 5 or more days each week. Include brisk walking.
   - I am not regularly physically active and do not intend to be so in the next 6 months
   - I am not regularly physically active but am thinking about starting in the next 6 months
   - I do some physical activity but not enough to meet the description of regular physical activity
   - I am regularly physically active but only began in the last 6 months
   - I am regularly physically active and have been so for longer than 6 months

6. Does anyone in your house smoke? [ ] Yes [ ] No

7. Do you smoke? [ ] Yes [ ] No

8. Have you had hay fever in the past 12 months? [ ] Yes [ ] No

9. Have you had eczema/itchy rash in the past 12 months? [ ] Yes [ ] No

10. Do you have asthma? [ ] Yes [ ] No

11. Do you have an ongoing cough? [ ] Yes [ ] No

12. Has a Doctor said, “you have asthma”? [ ] Yes [ ] No

13. Do you take medication for your asthma? [ ] Yes [ ] No

*If you have ticked YES to any of the questions in this box please fill in the questions on the next page.*
*If you ticked NO to both of the questions in this box you have finished, thank you for your time!*

Version 3 18112008
14. In the past 4 weeks, how often did your asthma prevent you from getting as much done at work, school or at home?

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

15. During the past 4 weeks, how often did you have shortness of breath?

- More than once a day
- Once a day
- 3 to 6 times a week
- Once or twice a week
- Not at all

16. During the past 4 weeks, how often did your asthma symptoms (wheeze, coughing, shortness of breath, chest pain or pain) wake you up at night or early in the morning?

- 4 or more nights a week
- 2 to 3 nights a week
- 1 night a week
- Less than 1 night a week

17. During the past 4 weeks, how often have you used your blue inhaler or reliever medication (for example Salbutamol®, Ventolin®, Asmol®, Airomir®, Bricanyl®)?

- 3 or more times a day
- 1 or 2 times a day
- 2 to 3 times a day
- Once a week
- Not at all

18. How would you rate your asthma?

- Not controlled
- Poorly controlled
- Somewhat controlled
- Well controlled
- Completely controlled

Please read the following and tick one box that best describes your asthma in the last 12 months.
(Please tick one box only)

- I have asthma attacks from time to time, but do not have symptoms of asthma between attacks. This is called episodic asthma.
- I have asthma attacks from time to time, but do have symptoms of asthma between attacks. These can be during the day or at night. This is called persistent asthma.

You have finished, thank you for your time!

Version 3 18112008
Author/s:
GIBSON, ANNE-MARIE

Title:
Respiratory function, exercise and ventilation distribution in late adolescence in survivors born extremely preterm or extremely low birth weight

Date:
2013

Persistent Link:
http://hdl.handle.net/11343/42140

File Description:
Respiratory function, exercise and ventilation distribution in late adolescence in survivors born extremely preterm or extremely low birth weight