BMJ Open Impact of extreme prematurity or extreme low birth weight on young adult health and well-being: the Victorian Infant Collaborative Study (VICS) 1991–1992 Longitudinal Cohort study protocol

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ABSTRACT

Introduction Infants born extremely preterm (EP, <28 weeks' gestation) or with extremely low birth weight (ELBW, <1000 g) in the era when surfactant has been available clinically are at high risk of health and developmental problems in childhood and adolescence. However, how their health and well-being may be affected in adulthood is not well known. This study aims to compare between EP/ELBW and normal birthweight (NBW) controls: (1) physical health, mental health and socioemotional functioning at 25 years of age and (2) trajectories of these outcomes from childhood to adulthood. In addition, this study aims to identify risk factors in pregnancy, infancy, childhood and adolescence for poor physical health and well-being in EP/ELBW young adults.

Methods and analysis The Victorian Infant Collaborative Study (VICS) is a prospective geographical cohort of all EP/ELBW survivors to 18 years of age born in the State of Victoria, Australia, from 1 January 1991 to 31 December 1992 (n=297) and contemporaneous term-born/NBW controls (n=262). Participants were recruited at birth and followed up at 2, 5, 8 and 18 years. This 25-year follow-up includes assessments of physical health (cardiovascular, respiratory and musculoskeletal), mental health and socioemotional functioning. Outcomes will be compared between the birth groups using linear and logistic regression, fitted using generalised estimating equations (GEEs). Trajectories of health outcomes from early childhood will be compared between the birth groups using linear mixed-effects models. Risk factors for adult outcomes will be assessed using linear and logistic regression (fitted using GEEs).

Ethics and dissemination This study was approved by the Human Research Ethics Committees of the Royal Women's Hospital, Mercy Hospital for Women, Monash Medical Centre and the Royal Children's Hospital, Melbourne. Study outcomes will be disseminated through conference presentations, peer-reviewed publications, the internet and social media.

Strengths and limitations of this study

- This is one of the first extremely preterm/extremely low birth weight cohorts worldwide born in the postsurfactant era with assessments across a broad range of outcomes in young adulthood.
- The geographical nature of the inception cohort minimises biases in cohort selection.
- The comprehensive assessments of the cohort throughout childhood to young adulthood (ages 2, 5, 8, 18 and 25 years) will enable not only *cross-sectional* analysis but also *longitudinal* assessments across a wide range of health outcomes.
- We expect some attrition at age 25 years and therefore will need to account for potential biases of those who return for follow-up compared with those who do not.
- We are unable to assess all important health outcomes due to time and resource constraints.

INTRODUCTION

Preterm birth, that is, birth prior to 37 completed weeks of gestation, is associated with greater mortality and long-term morbidity compared with being born full term (≥37 weeks' gestation).¹ The risks of mortality and morbidity are highest in the most immature and tiniest of infants, that is, those born extremely preterm (EP, <28 weeks' gestation) or with extremely low birth weight (ELBW, <1000 g).¹ Prior to the 1970s, survival rates of EP/ELBW infants were very low, in the order of <10%.² Since then, there have been key advances in 'modern perinatal/neonatal intensive care', notably, antenatal corticosteroids and assisted ventilation

in the 1970–1980s, and exogenous surfactant to treat respiratory distress syndrome in the newborn in 1991. Consequently, survival rates of EP/ELBW infants rose dramatically, for example, to 75% in the State of Victoria by the late 1990s.² The earliest EP/ELBW cohorts in the modern era from when surfactant became available are now reaching adulthood.

Compared with normal birth weight (NBW, birth weight ≥ 2500 g) or term-born controls, EP/ELBW survivors have higher rates of physical, socioemotional and mental health problems in childhood and adolescence.¹ Early childhood outcomes such as higher blood pressure (BP),³ poorer lung function⁴ and more behavioural/emotional problems⁵ in EP/ELBW survivors portend significant adult disease. However, outcomes into adulthood for EP/ELBW survivors from the modern era, after the introduction of surfactant, have not been described. Current knowledge of adult outcomes following EP/ELBW birth is derived predominantly from cohorts born in the 1970s.¹ These cohorts are systematically different from contemporary EP/ELBW survivors in that those from the 1970s were more mature or heavier at birth; the most immature infants (born 23–24 weeks) did not survive. Survival rates at 25–27 weeks were also much lower than survival rates today. Moreover, the spectrum of neonatal lung disease in the 1970s differed from that in the 1990s.⁶ In the 1970s, preterm newborns with acute lung disease were not treated with surfactant. Also, those who developed bronchopulmonary dysplasia, that is, inflammatory lung injury from mechanical ventilation, were not treated with antenatal corticosteroids.⁶ By the 1990s, surfactant became available for clinical use; the first baby was treated clinically with surfactant in March 1991 in the state of Victoria. Infants who developed bronchopulmonary dysplasia after surfactant was available had mainly abnormal alveolar formation rather than inflammation and were treated with large doses of postnatal corticosteroids,⁶ the long-term effects into adulthood are largely unknown.

While there are some limited adolescent data in contemporary EP/ELBW survivors, it is not sufficient to extrapolate outcomes from late adolescence into adulthood. Previous reports have documented higher BP,^{7,8} worse lung function^{9,10} and an increased risk for psychiatric diagnoses, including anxiety and depression,¹¹ although the finding of higher rates of anxiety and depression is not consistent across all cohorts, including the one included in this protocol.¹² However, self-esteem and quality of life in EP/ELBW adolescents were similar to those in controls.¹³ Specific health concerns, such as altered vascular compliance, abnormal insulin sensitivity and other issues relating to transition to adult life, may not manifest until the mid-20s. Moreover, the period of adolescence and young adulthood is one whereby maturation of many organ systems in the body is still occurring. The responses to the environment in general and mental health during the period between adolescence and young adulthood for those born EP/ELBW is not

well documented. It is therefore imperative to establish the health outcomes into adulthood of contemporary EP/ELBW survivors to inform healthcare providers of the true burden of illness in these individuals.

The proposed study will (1) provide vital information to inform physicians of specific adult health problems faced by EP/ELBW survivors compared with NBW term-born controls, (2) identify early life biomarkers and potentially other predictors of disease risk in EP/ELBW survivors, (3) form the basis for development of strategies for disease surveillance and (4) assist in designing health preventions and interventions to optimise the health and well-being of EP/ELBW for the rest of their lives.

OBJECTIVES

The overall aim of this study was to understand the impact and predictors of EP/ELBW on major aspects of health and well-being in young adults. The specific aims are to

1. Compare between EP/ELBW and NBW term-born control young adults in their mid-20s the following:
 - a. Physical health (cardiometabolic, respiratory and musculoskeletal).
 - b. Well-being, namely, mental health (depression, anxiety and substance use), socioemotional functioning (social skills, self-esteem and quality of life), education/employment, and transition to adult life.
2. Compare the trajectories of BP, vascular health, respiratory function, mental health and socioemotional functioning from childhood to adulthood between EP/ELBW and control groups.
3. Identify risk factors in pregnancy, infancy, childhood and adolescence for poor physical health and well-being in young adulthood in the EP/ELBW group, and determine whether socioeconomic exposures (social class and parental education), lifestyle factors such as smoking, diet and physical activity, academic achievement, employment, and social integration during childhood and adolescence moderate these relationships.

We hypothesise that:

1. Compared with controls, EP/ELBW young adults will have
 - a. Impaired vascular compliance, higher BP, reduced insulin sensitivity, unfavourable lipid profiles, impaired respiratory function, and inferior bone and muscle health.
 - b. More mental health problems, particularly behavioural and emotional regulation, poorer social functioning, lower educational attainment and higher unemployment; but equivalent self-esteem and quality of life.
2. BP, respiratory function and mental health will be worse at age 25 years. There will be a greater decline between 18 and 25 years in adults born EP/ELBW compared with controls, but will be similar for vascular health, social functioning, self-esteem and quality of life.

3. Risk factors for poor outcomes in young adulthood will be identifiable as early as the perinatal period. In particular, we expect bronchopulmonary dysplasia, treatment with postnatal corticosteroids and/or neonatal brain injury to be associated with poorer long-term outcomes. Furthermore, we expect that adverse social environments will be associated with stronger relationships between risk factors and poor outcome.

METHODS AND ANALYSIS

Design

This study is a prospective long-term follow-up of an established cohort.

Study population

The Victorian Infant Collaborative Study (VICS) 91–92 cohort is a geographical cohort of all EP/ELBW survivors to 25 years of age born in the State of Victoria between 1 January 1991 and 31 December 1992 (n=297) and contemporaneously recruited term-born NBW controls (n=260). This cohort is unique, with a wealth of recorded antenatal and perinatal information (eg, exposure to antenatal and postnatal corticosteroids, administration of surfactant, presence of brain injury, sepsis, surgery and bronchopulmonary dysplasia), as well as social and environmental data (eg, family structure, paternal and maternal education, paternal and maternal occupation and employment status and language spoken at home) at various ages from birth to 18 years. We have detailed comprehensive health and neuropsychological follow-up assessments of both EP/ELBW and controls at 2, 5, 8^{14–17} and 18 years of age,^{7 12 18 19} in particular, cardiovascular assessments, respiratory function, socioemotional, mental health and educational attainment. This protocol paper presents the details of the follow-up of this cohort in their mid-20s.

Study measures

Participants will attend a single-day follow-up visit at the Royal Melbourne Hospital and the Royal Children's Hospital, Melbourne. All assessors will be unaware of the birth group and results of earlier assessments.

1. Cardiovascular:

- a. BP: BP will be measured with an oscillometric device, as well as with an ambulatory BP machine to avoid 'white-coat' hypertension. Ambulatory BP systolic, mean and diastolic will be measured over 24 hours, including when awake and asleep. An activity/sleep diary will be provided to the participants to record their sleep and awake times.
- b. Arterial pulse wave velocity and pulse wave analysis: After fasting for at least 6 hours, arterial stiffness will be assessed by central and peripheral pulse wave velocity and pressure waveform analysis. All data will be acquired onto a personal computer using Sphygmocor XCEL calibrated to brachial BP. Simultaneous carotid/femoral waveforms will be acquired for the assessment of pulse wave velocity by the foot-to-

foot method.²⁰ Carotid waveforms will be analysed, in addition to central waveforms reconstructed by the application of a generalised arterial transfer function,²¹ and include augmentation index and pressure augmentation.

- c. Carotid intimal and intima-media thickness: Changes in the thickness of carotid artery wall layers will be measured by ultrasound. Images will be optimised to visualise the common carotid artery 1 cm proximal to the carotid bulb. BP in the right upper arm will be measured. A B-mode and an M-mode cine loop of five cardiac cycles will be recorded. To examine arterial distensibility, the maximal and minimal diameters of the vessel will be measured. The intima-media thickness of the far wall of this segment of the carotid artery will also be measured using digital callipers at end-diastole (R-wave of ECG). Pulse wave interrogation, with appropriate angle correction, of carotid artery blood flow will be made.
 - d. Heart rate variability: This will be used as a surrogate measure of autonomic nervous system activity. Data will be acquired using three ECG leads placed over the clavicles and the left lower ribs, with the participant lying in a quiet room for a duration of 15 min. Resting heart rate, heart rate variation on expiration and inspiration, and QT interval will be measured. Data will be analysed using time-domain and frequency-domain methods.
 - e. 'Cardiovascular risk factors': Factors that will be measured include insulin resistance (using fasting glucose and insulin concentrations), high-sensitivity C reactive protein and lipid profiles (ie, fasting cholesterol [total, low- and high-density lipoprotein] and triglycerides) and full blood count.
- #### 2. Respiratory:
- a. Spirometry will be measured according to standard guidelines of the American Thoracic Society. We will measure airflow (forced expired volume in 1 s (FEV₁), forced mid-expiratory flow [FEF_{25–75%}]) and reversibility using bronchodilators, lung volumes (forced vital capacity, total lung capacity and residual volume), and gas exchange (diffusing capacity of the lung for carbon monoxide).
 - b. Exercise tolerance will be assessed using the 6 min walk test and the BEEP test of cardiorespiratory fitness. For the 6 min walk test, the participants will be asked to walk at a normal pace for 6 min. The total distance walked and their maximal heart rate and lowest oxygen saturation will be measured. For the BEEP test, participants will walk/run over a set distance between two markers, first starting at a slower speed, with the speed then steadily increasing. The required tempo is determined by sequential beeps, which gradually sound closer together, requiring the participants to increase their speed. The test is completed once the participants are unable to keep up with the 'beeps'. Four common metrics will be reported, that is, speed at last completed stage,

number of completed stages/minute, number of completed laps and a calculated relative peak oxygen uptake from the other measured variables from the BEEP test.²²

- c. Respiratory health questionnaires: Participants will be asked to complete a standardised questionnaire, that is, the St George's Respiratory Questionnaire,²³ to determine respiratory health and impact on daily life associated with chronic obstructive airways disease and asthma. A total score is calculated, whereby 100 represents the worst health status and 0 indicates the best possible health status.
3. Musculoskeletal:
 - a. Bone mineral and soft tissue measurements: These will be measured using two methods. Peripheral quantitative computed tomography (XCT 3000; Stratec, Pforzheim, Germany) measures trabecular and cortical volumetric bone mineral density, bone geometry, indices of long bone strength, and tibial muscle cross-sectional area and muscle density at tibial sites. Dual energy X-ray absorptiometry (DXA Horizon, Hologic Inc, Bedford MA, USA) measures total body bone mineral content, hip and lumbar spine areal bone mineral densities and soft tissue composition.
 - b. Muscle function measurements: A Leonardo ground reaction force platform (Novotec, Pforzheim, Germany) will be used to measure muscle function (lower limb energy and power) and standardised balance test performance to evaluate possible late effects of brain injury, which is prevalent among EP/ELBW survivors.
 - c. Vitamin D nutritional status and circulating markers of bone turnover: serum 25 hydroxyvitamin D, serum procollagen type 1 N-terminal propeptide (marker of bone formation) and C-terminal telopeptide of type 1 collagen (marker of bone resorption).
 4. Mental health, emotional well-being and social functioning:

Mental health will be assessed both categorically and dimensionally with instruments previously used in this cohort to facilitate longitudinal analyses. Current and lifetime Axis I mood, anxiety and substance use disorders will be assessed by trained registered psychologists using the relevant modules of the Structured Clinical Interview for DSM-IV Axis I Non-Patient version.^{12 24} Current mood and anxiety symptoms will be assessed dimensionally using the Centre for Epidemiologic Studies Depression Scale-Revised²⁵ and the Beck Anxiety Inventory.²⁶ Age-appropriate assessment of attention deficit and hyperactivity disorder (ADHD) symptomatology will be conducted during face-to-face interview using the Adult ADHD Self-Report Scale (ASRS-v1.1) Symptoms Checklist.²⁷ Personality traits will be assessed using the NEO Five Factor Inventory-3²⁸ in order to measure more stable aspects of emotional functioning. Social functioning,

peer substance use, reproductive history and quality of life will be assessed using questions from the wave eight follow-up of the Victorian Adolescent Health Cohort Study²⁹ and the Health Utility Index.³⁰

Table 1 Potential confounding variables collected at different ages since infancy

	Age when data were collected	Aim where variable will be used
Perinatal and infant factors		
Gestational age	Birth	1, 2, 3
Birthweight z-score	Birth	1, 2, 3
Sex	Birth	1, 2, 3
Durations of assisted ventilation and oxygen therapy	Newborn period	1, 2, 3
Postnatal corticosteroids to treat or prevent bronchopulmonary dysplasia	Newborn period	1, 2, 3
Oxygen at 36 weeks' postmenstrual age	Newborn period	1, 2, 3
Major brain injury (either intraventricular haemorrhage Grade 3 or 4, or cystic periventricular leucomalacia)	Newborn period	1, 2, 3
Surgery during the primary hospitalisation	Newborn period	1, 2, 3
Sociodemographic family factors		
Maternal education (high vs low)	All ages	1
Social class (high vs low)	All ages	1
Childhood factors		
Height, weight and body mass index	2, 5 and 8 years	2, 3
BP	8 years	2, 3
Respiratory function	8 years	2, 3
Neurodevelopment	2, 5 and 8 years	2, 3
Adolescent factors		
Height, weight and body mass index	18 years	3
BP	18 years	3
Respiratory function	18 years	3
Vascular measures	18 years	3
Smoking status	18 years	3
Mental health	18 years	3
Socioemotional functioning	18 years	3
Young adult factors		
Height, weight and body mass index	25 years	1, 3
Smoking status	25 years	1, 3

BP, blood pressure.

Statistical considerations and power

Data will be stored in a study-specific database. Outcomes during adulthood will be compared between the groups using linear (continuous outcomes) and logistic (binary outcomes) regression, both unadjusted and adjusted for potential confounding variables, as listed in [table 1](#) (Aim 1). Models will be fitted using generalised estimating equations (GEEs) and reported with robust (sandwich) estimates of standard errors to allow for clustering of siblings within a family. Trajectories of development will be compared between the birth groups using linear mixed-effects models applied to the data across all time points. Models will include a random intercept and a random slope to allow for repeated measures within an individual, and fixed effects of time, group and a group×time interaction (Aim 2). Linear and logistic regression (fitted using GEEs) will be used to assess risk factors for adult outcomes (Aim 3). Initially, potential predictors will be explored using univariable regression, before combining predictors into a multivariable model to assess independent predictors. Social factors during childhood and adolescence will be assessed as mediators in these relationships by the addition of these factors to the multivariable regression models. Risk factors from the different ages are listed in [table 1](#). We anticipate that approximately 75% of the cohort will be followed up at the 25-year assessment based on the 18-year follow-up; this will result in 223 EPs/ELBW and 196 controls. There are 27 pairs of twins in the EP/ELBW group (18% of participants) and none in the control group. Assuming an intraclass correlation coefficient of 0.6 between outcomes for twins and 18% of the EP/ELBW group who attend the follow-up are twins (40 participants), this will result in an effective sample size of 201 EPs/ELBW. Samples of 201 EPs/ELBW and 196 controls will enable differences between the groups in the continuous outcomes as small as 0.28 SD to be detected, with 80% power (based on a two-sided t-test with $\alpha=0.05$). If only 60% of participants are assessed (effective sample size 162 EP/ELBW and 157 controls), we will still have 80% power to detect mean differences between the groups as small as 0.31 SD. For most continuous outcomes, differences of 0.28–0.31 SD between groups would be clinically important. For proportions, if the event rate is 50% in the controls, we will have 80% power to detect differences of $\pm 15\%$ (based on 75% follow-up). As the event rate moves away from 50%, we will have 80% power to detect slightly smaller absolute differences between the two groups.

Patient and public involvement

The development of the research question and outcome measures are based on the findings of our previous research into the health and developmental outcomes of EP/ELBW from infancy to late adolescence.^{2 7 9–14 16 17} The importance of long-term outcomes was discussed in a workshop sponsored by our National Health and Medical Research Council-funded Centre of Research Excellence in Newborn Medicine, which included parent

representatives.³¹ However, there was no direct involvement of EP/ELBW individuals or their families in the design of the study.

Ethics and dissemination

Study outcomes will be disseminated through conference presentations, peer-reviewed publications, the internet, and social media. All participants will receive a written summary of their assessments and, if required, clinical follow-up through their primary health physician or other appropriate clinical service will be offered.

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Contributors JLYC conceived and designed the study, drafted and critically revised the manuscript and gave the final approval of the version to be published. JDW, MMC, LI, KJL, SMG, DS and GCP conceived and designed the study, critically revised the manuscript and gave the final approval of the version to be published. ACB conceived and designed the study, acquired the data, critically revised the manuscript and gave the final approval of the version to be published. AH acquired the data, critically revised the manuscript and gave the final approval of the version to be published. LWD conceived and designed the study, critically revised the manuscript and gave the final approval of the version to be published.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The original and follow-up studies of this cohort were approved by the Human Research Ethics Committees of all the four centres in the state of Victoria, Australia that have neonatal intensive care nurseries, ie, the Royal Women's Hospital, Mercy Hospital for Women, Monash Medical Centre and the Royal Children's Hospital, Melbourne.

Provenance and peer review Not commissioned; peer reviewed for ethical and funding approval prior to submission.

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