Cardiac cycle: an observational/interventional study protocol to characterise cardiopulmonary function and evaluate a home-based cycling program in children and adolescents born extremely preterm

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**ABSTRACT**

Introduction Extremely preterm (EP)/extremely low birthweight (ELBW) individuals may have an increased risk for adverse cardiovascular outcomes. Compared with term-born controls, these individuals have poorer lung function and reduced exercise capacity. Exercise interventions play an important role in reducing cardiopulmonary risk, however their use in EP/ELBW cohorts is unknown. This study, cardiac cycle, aims to characterise the cardiopulmonary system of children and adolescents who were born EP compared with those born at term, following acute and chronic exercise bouts.

Methods and analysis The single-centre study comprises a home-based exercise intervention, with physiological characterisation at baseline and after completion of the intervention. Fifty-eight children and adolescents aged 10–18 years who were born EP and/or with ELBW will be recruited. Cardiopulmonary function assessed via measures of blood pressure, arterial stiffness, capillary density, peak oxygen consumption, lung clearance indexes and ventricular structure/function, will be compared with 58 age-matched and sex-matched term-born controls at baseline and post intervention. The intervention will consist of a 10-week stationary cycling programme, utilising Zwift technology.

Ethics and dissemination The study is approved by the Ethics Committee of the Royal Children’s Hospital Melbourne under HREC2019.053. Results will be disseminated via peer-reviewed journal regardless of outcome.

**STRENGTHS AND LIMITATIONS OF THIS STUDY**

⇒ This study will constitute the most comprehensive characterisation of cardiopulmonary physiology in children/adolescents born extremely premature/extremely low birth weight.

⇒ We describe a novel home-based exercise intervention that avoids multiple weekly hospital/clinic visits over a 10-week period and uses technology to both maximise engagement and enable remote tracking of progress.

⇒ The intervention can only be conducted in those physically able to perform cycling exercise.

⇒ Our study focuses on physiological responses to the exercise intervention and is not designed for long-term follow-up.

**INTRODUCTION**

Extremely preterm birth and cardiopulmonary outcomes

With one in every 10 babies born preterm, the estimated number of extremely preterm (EP, <28 weeks’ gestation) births is approximately 15 million per year worldwide. Due to advances in perinatal and neonatal care, the mortality rate of EP and/or extremely low birth weight (ELBW, birth weight <1000 g) has decreased substantially, with rates of survival reported at 87% in the developed world. While more EP/ELBW individuals are surviving to adolescence and adulthood, there is relatively limited evidence describing the long-term health outcomes of this population.

Preterm birth exposes the cardiovascular system to extrauterine conditions before the anatomy has fully matured. A growing number of studies indicate that the long-term consequences of this include increased arterial stiffness, altered ventricular structure, decreased capillary bed perfusion and increased blood pressure (BP) as measured in childhood and adulthood. The association between very preterm (VP; <32 weeks’ gestation) and higher arterial BP is in the order of 5.4 mmHg higher systolic BP and a 4.2 mmHg higher diastolic BP than
term-born controls. This seemingly small difference is clinically important, as a 2 mmHg reduction in diastolic BP in adults can reduce the risk of coronary heart disease by 6%, and risk of cerebrovascular events by 15%. Further, children with higher BP appear to have steeper BP trajectories into mid-life. Importantly, for a pulmonary parenchyma is developing during the saccular stage (27–36 weeks) of lung development. At this stage, the pulmonary parenchyma is developing into saccules, eventually becoming alveolar ducts and the diffusion site for capillary beds. Importantly, for a full-term pregnancy, about 90% of neonate’s alveoli are formed after birth, with evidence that the lungs continue to develop postnatally. With preterm birth, survival is often dependent on treatments where assisted ventilation and oxygen supplementation occur. Hence, while these treatments are life-saving, they may disturb further lung development and have a life-long impact on lung function.

Exercise

One of the most effective approaches for characterising the cardiopulmonary system and reducing cardiovascular disease risk is exercise. A single bout of acute submaximal and/or maximal exercise can assist in evaluating disease risk, reveal underlying pathology and establish functional capacity. In addition, higher cardiorespiratory fitness and lifestyle physical activity lower the risk of all-cause mortality and chronic disease, mitigate associated symptoms and improve functional capacity. These multi-systemic adaptations associated with chronic exercise optimise physiologic function, increase longevity, health, and quality of life. Although O’Dea et al recently reported evidence that preterm birth impairs lung function, but not exercise capacity, a number of other studies suggest that preterm birth does impair exercise capacity compared with term-born controls. Earlier preterm birth may be associated with decreases in physical fitness, anaerobic threshold and work rate, a higher respiratory exchange ratio at a lower heart rate and a higher resting oxygen consumption at rest. EP and ELBW individuals demonstrate the highest reduction in physical fitness. The mechanistic basis of this reduced physical fitness has yet to be established in preterm birth/low birthweight individuals. While the aforementioned studies describe functional impairments and exercise limitations, these outcomes are based on investigations of the effect of an acute bout of exercise. The cardiopulmonary response to chronic exercise training (repeated bouts of exercise over a period of time) in EP/ELBW individuals is unknown. In fact, the only existing literature regarding exercise interventions in EP cohorts focuses on bone density and range of motion manipulation during infancy.

Exercise may be a promising intervention for improving cardiovascular function, pulmonary function and exercise capacity, all of which may be negatively associated with preterm birth. A recent meta-analysis reported that exercise interventions significantly increased both cardiovascular function and quality of life, and slightly increased pulmonary function, in children with chronic respiratory disease. In addition, chronic exercise has been shown to promote microvascular proliferation, improve forced expiratory volume per second and forced vital capacity, decrease systolic and diastolic BP and initiate favourable arterial remodelling. Given that physical activity behaviours track from childhood to adulthood, childhood and adolescence are ideal time to implement exercise interventions, as a strategy to prevent later adverse cardiopulmonary outcomes. However, the potential effect of such interventions in the EP/ELBW population is unknown.

Aims

Cardiac cycle aims to (1) compare the response of EP/ELBW participants to an acute bout of exercise with age-sex-matched, term-born controls, and (2) compare the effect of chronic exercise on cardiopulmonary physiology of EP/ELBW participants with age-sex-matched, term-born controls (figure 1). Specifically, we aim to:

2. Examine cardiopulmonary function (BP, resting heart rate, pulse wave velocity, heart rate variability (HRV), lung capacity) and aerobic fitness (VO2) in children and adolescents born EP/ELBW compared with term-born controls following an exercise intervention. Secondary aims are to:

1. Determine if there is a difference in pulmonary arterial pressure in EP/ELBW children and adolescents compared with term-born controls under resting and exercising conditions.
2. Characterise ventricular function and structure in EP/ELBW children and adolescents compared with term-born controls under resting and exercising conditions.
Characterise differences in aortic geometry (ascending aortic diameter, descending aortic diameter, and their ratio, ie, aortic tapering) between EP/ELBW participants and term-born controls.

Characterise physical activity behaviours and health-related quality of life of EP/ELBW individuals compared with term-born controls.

METHODS AND ANALYSES

Trial design
This study is an approved trial that has been registered with the Australia New Zealand Clinical Trial Registry. The start date of this study is not finalised due to current uncertainties and restrictions related to the COVID-19 pandemic. The investigation is a non-randomised, single-site study examining cardiopulmonary function and exercise capacity in children and adolescents born EP/ELBW, compared with term-born controls. Both EP/ELBW and controls will complete baseline assessments, a 10-week exercise intervention and follow-up assessments (Figure 1). Patients and public were not involved in the design of this protocol.

Participants and recruitment
Fifty-eight aged individuals born EP/ELBW and 58 age-sex-matched term-born controls will be identified and recruited through the Victorian Infant Collaboration Study (VICS) cohort in Melbourne, Australia. Participants will be included if they are:

1. Individuals born EP/ELBW between the ages of 10 and 18 years.
2. Age-matched and sex-matched individuals born at term (>37 weeks, term-born controls)
3. Are deemed high risk for cardiovascular, metabolic or pulmonary disease based on the Exercise and Sport Science Australia Pre-Exercise Screening System.
4. Are taking, or have taken within 6 weeks, antihypertensive medication prior to study commencement.
5. Are unable to ride a stationary bike for 20 minutes.
4. Are unable to independently follow a sequence of written and verbal instructions in English.
5. Have impaired lung function, defined as a forced expiratory volume per second <65% of their predicted value.

Existing participants of the VICS will be invited to participate in the study. All interested participants will complete a comprehensive screening process with a member of the research team to determine their eligibility to take part and if deemed eligible informed consent will be obtained by the parents/guardians. Participants have the option to opt out at any point of the study.

Intervention
‘Cardiac cycle’ will consist of a 10-week stationary cycling exercise programme, with progressively increasing frequency, time and intensity over the course of the intervention (Table 1). The following exercise prescription is based on the American College of Sports Medicine guidelines. The intervention will consist of three types of aerobic sessions. These include (1) steady-state cycling, where participants will maintain the same intensity throughout the entire session, (2) tempo cycling, similar to steady-state cycling, where participants will have an increased intensity for the duration of the session (excluding warming up and cool down) and (3) interval cycling, where participants will alternate between high intensity and low intensity for the duration of session.

Participants will complete 2–3 exercise sessions per week for 10 weeks (27 sessions total).

Following physiological characterisation, a member of the research team will complete a home visit to deliver all equipment and assist in the setup of a bike trainer (Blue Matic Trainer, TACX, Wassenaar, Netherlands). The smart bike trainer attaches to the rear axle of the participants’ personal bike, converting it into a stationary bike; alternatively, a bike will be provided if the participant does not own one. Participants will be provided with a heart rate monitor.
Table 1  Sample of 10-week training programme

<table>
<thead>
<tr>
<th>Week</th>
<th>Frequency</th>
<th>Session 1: steady state</th>
<th>Session 2: intervals</th>
<th>Session 3: tempo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Week 1</td>
<td>Two sessions</td>
<td>20 min at 55% HRR</td>
<td>▶ 5 min warm up</td>
<td>▶ 5 min warm up.10 min at 75% HRR</td>
</tr>
<tr>
<td>Week 2</td>
<td>Two sessions</td>
<td>20 min at 55% HRR</td>
<td>▶ 5 min warm up</td>
<td>▶ 5 min warm up.10 min at 75% HRR</td>
</tr>
<tr>
<td>Week 3</td>
<td>Two sessions</td>
<td>20 min at 55% HRR</td>
<td>▶ 5 min warm up</td>
<td>▶ 5 min warm up.10 min at 75% HRR</td>
</tr>
<tr>
<td>Week 4</td>
<td>Three sessions</td>
<td>20 min at 60% HRR</td>
<td>▶ 5 min warm up</td>
<td>▶ 5 min warm up.10 min at 75% HRR</td>
</tr>
<tr>
<td>Week 5</td>
<td>Three sessions</td>
<td>20 min at 65% HRR</td>
<td>▶ 5 min warm up</td>
<td>▶ 5 min warm up.10 min at 75% HRR</td>
</tr>
<tr>
<td>Week 6</td>
<td>Three sessions</td>
<td>20 min at 65% HRR</td>
<td>▶ 5 min warm up</td>
<td>▶ 5 min warm up.10 min at 75% HRR</td>
</tr>
<tr>
<td>Week 7</td>
<td>Three sessions</td>
<td>20 min at 70% HRR</td>
<td>▶ 5 min warm up</td>
<td>▶ 5 min warm up.10 min at 70% HRR</td>
</tr>
<tr>
<td>Week 8</td>
<td>Three sessions</td>
<td>20 min at 70% HRR</td>
<td>▶ 5 min warm up</td>
<td>▶ 5 min warm up.10 min at 70% HRR</td>
</tr>
<tr>
<td>Week 9</td>
<td>Three sessions</td>
<td>20 min at 70% HRR</td>
<td>▶ 5 min warm up</td>
<td>▶ 5 min warm up.10 min at 70% HRR</td>
</tr>
<tr>
<td>Week 10</td>
<td>Three sessions</td>
<td>20 min at 70% HRR</td>
<td>▶ 5 min warm up</td>
<td>▶ 5 min warm up.10 min at 70% HRR</td>
</tr>
</tbody>
</table>

Session 1: steady state
- Frequency: Two sessions
- Session 1: steady state: 20 min at 55% HRR
- Session 2: intervals:
  - 5 min warm up
  - 2 sets, 8 reps 10 s high intensity, 20 s active recovery
  - 2 min active recovery between sets
  - 5 min warm down

Session 2: intervals
- Frequency: Three sessions
- Session 3: tempo:
  - 5 min warm up.10 min at 75% HRR
  - 5 min warm down

Total volume: 540 minutes. The number of sessions the individuals complete will be used as a covariable in the analyses of the effects of exercise. HHR, heart rate reserve.
rate monitor (Wahoo Fitness, Atlanta, Georgia, USA) and instructed to wear this around the inner forearm during exercise sessions. They will also be provided a speed sensor (Wahoo Fitness, Atlanta, Georgia, USA) which is attached to the rear axle of the bike. Both the heart rate monitor and speed sensor will transmit data onto a computer, phone or tablet where the participants can monitor their effort, with information also used by the researchers to monitor adherence to the exercise programme as described below.

Participants will use Zwift (Zwift, Long Beach, California, USA), a non-immersive virtual reality cycling app that allows participants to travel along interesting roads/paths in real or imaginary locations. After the completion of each training session, the data from Zwift will automatically upload onto Strava (Strava, San Francisco, California, USA), allowing the research team to access the data from each session via Strava’s cloud storage. Additionally, Strava allows the researcher to monitor adherence to the exercise protocol.

**PROCEDURE**

Outcome measure assessment and timing is summarised in figure 1, and a detailed overview of each measure is provided at the end of this section. Baseline testing will occur over two sessions. One session will occur at the participants’ home and one session at the Royal Children’s Hospital (58 EP/ELBW and 58 term-born controls). On completion of the 10-week home-based exercise training programme, outcomes will be assessed within a week postintervention in an additional hospital-based session (58 EP/ELBW and 58 term-born controls).

<table>
<thead>
<tr>
<th>Measure</th>
<th>Domains</th>
<th>What is scored</th>
<th>Assessed by</th>
<th>Validation</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Youth Activity Profile</td>
<td>Physical activity during school</td>
<td>Frequency of physical activity as transport to and from school, duration of physical activity during school, frequency of physical activity outside of school, duration of physical activity outside of school, duration of sedentary activity</td>
<td>Self-assessment over the past 7 days</td>
<td>YAP has been validated in school aged children in the USA, and has been validated for sedentary and moderate to vigorous physical activity.</td>
</tr>
<tr>
<td>Paediatric Quality of Life Inventory</td>
<td>Health-related quality of life in healthy children and adolescents and those with acute and chronic conditions</td>
<td>Positive and negative perceptions of physical, emotional, social and school functioning; Likert scale</td>
<td>Self-assessment and parental assessment over the past month</td>
<td>PedsQL has been validated in 2-year-old to 18-year-old Americans and is considered acceptable for clinical trial usage. There are parallel forms for parents and child/adolescent. Coordination between parent/guardian and child/adolescent is imperfect.</td>
</tr>
<tr>
<td>Exercise Regulations Questionnaire (BREQ-2)</td>
<td>Decisions for participating in exercise (19 items)</td>
<td>Positive perceptions towards participating in exercise, negative perceptions towards participating in exercise; Likert scale</td>
<td>Self-assessment</td>
<td>BREQ-2 has been validated in adults, overweight high school aged students and obese 15-year-old adolescents.</td>
</tr>
</tbody>
</table>

Baseline assessment (home)

Participants will receive an ActiGraph GT3X accelerometer (ActiGraph, Pensacola, Florida) to measure habitual physical activity over 7 days. This will be completed prior to attending the hospital visit.

Baseline assessment (hospital)

Participants will be given a link to an online REDCap form comprising three questionnaires (table 2) relating to exercise behaviours and quality of life. Both a researcher and parent and/or guardian will be in the room with the participant while they complete the surveys.

An overview of the hospital-based testing is shown in figure 2. For the purposes of this study, imaging technologists and respiratory scientists will be blinded from gestational age during data acquisition. After recording height, weight, body mass index and estimated percent body fat (via bioelectrical impedance analysis), participants will rest for 5 min in the supine position, before undergoing a battery of cardiovascular measurements including HRV, bilateral brachial BP measurement, estimated central BP, aortic stiffness, carotid arterial stiffness and capillary density and perfusion. Participants will proceed to the respiratory lab for lung function tests including multiple breath washout, spirometry, plethysmography, airway reversibility and a cardiopulmonary exercise peak test with a pretranssthoracic and post-transsthoracic echocardiogram. Lastly, participants will undergo a cardiac MRI with a recumbent cycling component.

Testing duration for the hospital visit will last approximately 6 hours, including a 1-hour break.
Exercise intervention

The intervention consists of 27 home-based stationary cycling sessions (table 1). Data on numbers of sessions attended and completed in accordance with the protocol will be recorded and continuously monitored through the Strava software. A research assistant will check in with the participants weekly via phone or email.

Postintervention assessment

The post intervention visit will take place within 1 week of the final exercise session. All home-based and hospital-based assessments outlined in the baseline assessment will be repeated, excluding the exercise MRI as cardiac structure is not expected to change during a 10-week exercise intervention. An accelerometer will be fitted as in the baseline assessment and returned after 1 week.

OUTCOME MEASURES

Primary outcomes

Resting demographics and haemodynamic measurements

The cardiovascular battery will begin with a 10-min recording of HRV via a three-lead ECG. Data will be recorded on a PowerLab data acquisition system and analysed on LabChart Pro 8 and (AD Instruments, Sydney, Australia) for average resting heart rate, root mean square of the successive differences for the R–R intervals, high frequency domain, low frequency domain and very low frequency domain for metrics of parasympathetic activity. Central pressure will be assessed by radial tonometry (SPT-301, Millar Instruments, Houston, USA) and a transfer function, a validated method in children and adults. Two consecutive measures of simultaneous bilateral BP will be recorded using Watch BP Office Central (Microlife, Widnau, Switzerland). Two measures of carotid-femoral pulse wave velocity will be measured by SphygmoCor XCEL (AtCor, West Ryde, Australia). Carotid intima media thickness, diameter, distensibility, and blood flow will be measured using vascular ultrasound. Sublingual dermal capillary density and capillary blood flow will be assessed via a Cytocam LED microvascular camera (Braedius Medical, Huizen, Netherlands).

Respiratory testing

Lung clearance index will be calculated from multiple breath washouts based on methods described by Horsley. Spirometry and plethysmography will be measured using standard guidelines of the American Thoracic Society for measures of expiratory flow (forced expiratory flow in 1 s), lung volumes (forced vital capacity; total lung capacity; residual volume), functional residual capacity, reversibility (with bronchodilator for determining reversible airway obstruction), and gas exchange (diffusing capacity of the lung for carbon monoxide, DLCO (alveolar-capillary diffusing capacity)).

VO₂peak testing

Participants will have a transthoracic echocardiogram to estimate systolic, diastolic and mean pulmonary arterial pressure using methods reviewed by Parasuraman et al. Participants will then undergo a peak exercise stress test using a continuous ramping protocol to determine anaerobic threshold, peak oxygen and uptake (VO₂peak). Participants will begin with the cycle unloaded for the first 2 min. The resistance will continuously increase until volitional fatigue is reached. 12-lead ECG monitoring will be used to monitor heart rate. BP cuffs will be worn during the test to allow measurement of BP immediately after cessation of exercise. Data collected from the test will include measures of peak oxygen consumption, heart rate, workload, respiratory exchange ratio and oxygen pulse (a surrogate measure of stroke volume). Immediately after the peak test, a post-transthoracic echocardiography will be performed to determine peak exercise pulmonary pressures.

Exercise MRI

A standard cardiac MRI (1.5 Tesla Siemens, Philips, NSW, Australia) protocol will be used to examine cardiopulmonary structure and function at rest. Following the resting measurements, participants will be asked to cycle on an MRI-compatible cycle ergometer at a moderate cadence (70 rpm) with workload increasing until the participant has reached 70% of their peak workload determined from the cardiopulmonary exercise peak test. Real-time MRI sequences will be employed during exercise to minimise acquisition time and respiratory artefact.
Secondary outcomes
Habitual physical activity
Participants will wear an ActiGraph GT3X (ActiGraph, Pensacola, Florida, USA) for 1 week (including a minimum of 3 weekdays and 1 weekend day) before attending hospital baseline testing. The ActiGraph GT3X captures raw acceleration data, which is converted into information on activity counts, energy expenditure, metabolic equivalent rates, steps taken and physical activity intensity. Wear time will be calculated based on wear time validation algorithms.55 As there are no validated intensity cut-points specific to children and adolescents born EP/ELBW, recommended cut-points for healthy children will be used.55 56

Questionnaires
Participants will be asked to complete three questionnaires relating to health-related quality of life, physical activity and sedentary behaviours, and motivation to exercise. Details including psychometrics are described in table 2.

MONITORING ADVERSE EVENTS
Hospital visits
Prior to data collection, participants will be screened for exercise contraindications using the Exercise & Sport Science Australia Pre-Screening System.57 Hospital-based data collection will be supervised by the research coordinator and at least one other research assistant. If the research coordinator or research assistant determines that a cardiovascular measurement is outside of the normal and/or healthy range for the participants age, the results will be shown to the overseeing cardiologist. If the research coordinator or research assistant determines that a respiratory measurement is outside of the normal and/or healthy range for the participants age, the results will be shown to the overseeing respiratory physician/scientist. The overseeing cardiologist and/or respiratory physician will determine if the results merit referral for further clinical assessment.

Exercise intervention
Technique and safety procedures including mounting the bicycle, training, and dismounting the bicycle will be explained by the research team at the home visit, and participants will be given an instruction manual and supplementary video. Session attendance will be recorded, and participants will be encouraged to make up any missed sessions in the following week (where possible). Exercise training data will be uploaded onto Strava and monitored by the research team, in addition to weekly check-ins to monitor exercise tolerance and adverse events.

STATISTICAL ANALYSIS
For the purpose of this study, the participants will be assigned a corresponding code number, researchers will be blinded from gestational age during extraction/analysis.

Sample size
The sample of 116 subjects comprises 58 term-born controls and 58 EP/ELBW subjects. There is an estimated retention rate of 70%.58 Assuming a mean change in systolic pressure of 4 mmHg (SD 8 mmHg) for EP/ELBW and term-born controls a mean change of 0 mmHg (SD 4 mmHg) a sample size of 80 comprising of 40 EP/ELBW subjects and 40 term-born controls will have a power of 80% and an effect size of at least 0.6 (α=0.05).39

Analysis between groups at baseline
Baseline comparisons of cardiopulmonary function will be performed with 2-sample t-tests for each measurement if the data are normally distributed, or a Wilcoxon matched-pairs signed rank test if the data are non-normally distributed. All estimates will be reported with the corresponding 95% CIs.

Analysis between groups preintervention/post intervention
Comparisons of variables pre versus post exercise intervention will be completed using repeated measures one-way analysis of variance (ANOVA) with Tukey’s multiple comparisons for normally distributed data, or a Kruskal-Wallis test using Dunn’s multiple comparisons for non-normally distributed data. All estimates will be reported with the corresponding 95% CIs.

Analysis of questionnaires
Comparisons of physical activity behaviours, motivation and quality of life within and between groups will be completed using multiple comparisons one-way ANOVA with Tukey’s multiple comparisons. Data obtained from the baseline testing will also be used, in conjunction with the survey responses via regression analysis, to determine if there are correlations between habits of physical activity and exercise, and the underlying physiological disparities already identified between cohorts.

ETHICS AND DISSEMINATION
Ethics approval and trial registration
This study (HREC/51560/RCHM-2019) received approval from The Royal Children’s Hospital (Melbourne) Human Research Ethics Committee (HREC EC00238). The trial has been registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12619000539134). Participants and parent(s)/guardian(s) will receive information statements and will be given an opportunity to ask questions; participation can be discontinued at any point throughout the study. Informed written consent will be obtained from the parent(s)/guardian(s) and verbal assent from the participant. The Human Research Ethics Committee and Australian and New Zealand Clinical
Trials Registry will be amended for changes in protocol. Participants will be contacted if changes in protocol occur.

Data monitoring
Individual data will be monitored by the principal investigator during the appointments, intervention and on completion of the study. A data monitoring committee has been established comprising the principle investigator, the overseeing cardiologist and the research group’s biostatistician and will have access to the final trial dataset. Quarterly auditing of the study will be completed by the investigators.

Adverse events will be identified and documented by the study investigators over the course of the study. Participant data will be stored on a secure password-protected network drive. The study will be concluded once the target sample size has been reached.

Dissemination of findings
The study’s findings will be disseminated in the form of publication in peer-reviewed journals and conferences, and an overview of the main group results will be communicated to study participants. Results of this study will be published regardless of the direction or magnitude of the findings. The decision to release and/or publish any interim results will be made by the principle investigator.

DISCUSSION
Cardiac cycle will establish whether functional limitations of the cardiopulmonary system are modifiable with exercise for children and adolescents born EP/ELBW. Survival of individuals born EP/ELBW has increased substantially and there is a rapidly increasing population surviving into adulthood. Although evidence of long-term outcomes is limited, cardiopulmonary indicators of risk including increased BP, increased capillary density, and increased sympathetic activity at a young age are concerning. Characterising the cardiopulmonary and exercise status of this cohort will provide surrogate markers of long-term health outcomes of EP/ELBW birth and a means for assessing the efficacy of the exercise intervention.

Childhood into adolescence is a critical developmental period when physical activity tends to drastically decrease with a consequent increase in sedentary behaviour. Cardiac cycle makes use of technology (virtual bike riding app, fitness app and Bluetooth-connected bike/heart rate monitors) to create an engaging and motivating experience, while providing an avenue for remote monitoring of adherence and physiological responses to exercise. While this study focuses on understanding the impact of exercise on cardiopulmonary physiology, our technology-aided approach has potential application in other contexts, such as other clinical cohorts and rural and remote healthcare.

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Contributors MMC is the principle investigator and drafted the manuscript. CW and MMC conceived and designed the exercise intervention. JC leads the VICS cohort study. MMC, JPM and MMC conceived and designed the physiological and imaging investigations. All authors contributed to overall study design, edited the manuscript and approved the final version.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

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