Physiological responses to exercise in survivors of preterm birth: a meta-analysis

Michael L. Beaven [1,2], James T.D. Gibbons [1,2,3], Christopher W. Course [4], Sarah J. Kotecha[4], Thomas Hixson[5], Andrew Maiorana[1,6], Melissa Zuidersma[3], Sailesh Kotecha [4], Elizabeth F. Smith[1,2] and Shannon J. Simpson[1,2]

[1]Curtin School of Allied Health, Curtin University, Perth, Australia. [2]Children's Lung Health, Wal-yan Respiratory Research Centre, The Kids Research Institute Australia, Perth, Australia. [3]Department of Respiratory Medicine, Child and Adolescent Health Service, Perth Children's Hospital, Perth, Australia. [4]Department of Child Health, School of Medicine, Cardiff University, Cardiff, UK. [5]Regional Neonatal Intensive Care Unit, University Hospital of Wales, Cardiff, UK. [6]Department of Allied Health, Fiona Stanley Hospital, South Metropolitan Health Service, Perth, Australia.

Corresponding author: Shannon J. Simpson (shannon.simpson@thekids.org.au)

Shareable abstract (@ERSpublications)
This meta-analysis comprehensively summarises the physiological response to exercise in survivors of preterm birth over the lifespan, revealing key respiratory, cardiovascular and metabolic deficits at peak exercise. https://bit.ly/4hmcehh

Cite this article as: Beaven ML, Gibbons JTD, Course CW, *et al*. Physiological responses to exercise in survivors of preterm birth: a meta-analysis. *Eur Respir Rev* 2025; 34: 240163 [DOI: 10.1183/16000617.0163-2024].

Received: 18 July 2024
Accepted: 11 March 2025

Abstract

Rationale Survivors of preterm birth (<37 weeks' gestation) have low peak oxygen uptake, a global measure of aerobic fitness and an established predictor of increased morbidity and mortality. However, little is known about other cardiopulmonary outcome measures in this population. We addressed the hypothesis that preterm birth is associated with abnormal respiratory, cardiovascular and metabolic responses to exercise, as assessed by cardiopulmonary exercise testing, *via* a systematic review and meta-analysis.

Methods Six databases were systematically searched up to 29 November 2024 (PROSPERO: CRD42022320775). Studies reporting cardiopulmonary outcome measures obtained during a standardised exercise test were included if they had preterm-born participants and matched term-born controls. The standardised mean difference (SMD) between pooled preterm-born and term-born cohorts was calculated using random-effects models for the meta-analysis.

Results Of the 12 143 records identified, 47 cohorts were included in the final meta-analysis. At peak exercise, the preterm-born cohort (n=2149) demonstrated lower oxygen uptake (SMD −0.39, 95% CI −0.52 to −0.26), work rate (SMD −0.53, 95% CI −0.70 to −0.35), minute ventilation (SMD −0.43, 95% CI −0.60 to −0.26), tidal volume (SMD −0.38, 95% CI −0.62 to −0.15), oxygen pulse (SMD −0.47, 95% CI −0.75 to −0.19), heart rate (SMD −0.18, 95% CI −0.28 to −0.07), anaerobic threshold (SMD −0.29, 95% CI −0.49 to −0.08) and gas exchange efficiency (SMD 0.22, 95% CI 0.04 to 0.41), compared to the term-born cohort (n=1650).

Conclusions In addition to a reduced peak oxygen uptake, survivors of preterm birth have impairments in the respiratory, cardiovascular and metabolic domains during cardiopulmonary exercise testing. Given that reduced aerobic capacity is associated with increased morbidity and mortality, exercise interventions that target cardiorespiratory fitness should be prioritised across the lifespan in those born preterm.

Introduction

Respiratory system deficits are observed in children and adults born preterm, and are often amplified in those with a neonatal diagnosis of bronchopulmonary dysplasia (BPD) [1]. BPD is generally determined by the duration of respiratory support required in the neonatal intensive care unit. Significant advancements in perinatal care, such as the introduction of exogenous surfactant and antenatal corticosteroids in the early 1990s (*i.e.* the contemporary or post-surfactant era) have resulted in an altered BPD phenotype [2]. Our series of systematic reviews evaluating lung function across the lifespan for survivors of preterm birth have

shown reduced forced expiratory volume in 1 s [3], airway obstruction that may be progressing with increasing age [4], impaired gas transfer capacity and increased gas trapping in those born preterm when compared to term-born counterparts [5].

While routinely performed in the clinical setting and vitally important for monitoring the progression of lung disease, the above-mentioned lung function tests all examine the respiratory system at rest and consider the lung in isolation. However, survivors of preterm birth also have increased risk of developing chronic metabolic disorders (*e.g.* obesity, diabetes and metabolic syndrome) [6] and cardiovascular disease (*e.g.* hypertension and heart failure) [7, 8], concurrent with the increased risk of prematurity-associated lung disease [2], highlighting deficits across multiple links of the oxygen transport chain.

Peak oxygen consumption (peak $\dot{V}_{O_2}$) is a global measure of aerobic capacity and cardiorespiratory fitness, and a well-established predictor of all-cause morbidity, mortality and quality of life [9]. Peak $\dot{V}_{O_2}$ is of clinical interest because this population has increased cause-specific mortality from respiratory, endocrine and cardiovascular disorders and a 5-fold increased risk of all-cause mortality from birth to age 45 years [10]. Peak $\dot{V}_{O_2}$ can be accurately measured through breath-by-breath analysis during cardiopulmonary exercise testing (CPET). Previous meta-analyses in 2015 (children and adults) [11] and 2023 (adults only) [12] reported reduced peak $\dot{V}_{O_2}$ in those born preterm compared with term-born controls (mean difference -2.20 mL·min^{-1}·kg^{-1}, 95% CI -3.70 to -0.70 mL·min^{-1}·kg^{-1} and -3.84 mL·min^{-1}·kg^{-1}, 95% CI -5.61 to -2.07 mL·min^{-1}·kg^{-1}, respectively). However, in addition to peak $\dot{V}_{O_2}$, CPET provides information about how the respiratory, cardiovascular and metabolic systems respond to increased energy demands during exercise [6]. Studies reporting additional CPET outcomes are now published in survivors of preterm birth, with varying results [13–21]. However, small sample sizes and heterogenous study designs have hampered the interpretation of these outcomes in those born preterm. Given what we understand about the heterogenous sequelae of preterm birth, CPET outcomes beyond peak $\dot{V}_{O_2}$ could prove useful in understanding the range of possible physiological impacts of preterm birth. Surprisingly, there is yet to be a study summarising detailed CPET outcome data beyond that of peak $\dot{V}_{O_2}$ for this population.

To test the hypothesis that survivors of preterm birth have impaired physiological responses to exercise, we present a comprehensive meta-analysis of CPET outcomes extracted from a systematic review of CPET studies in preterm participants. The primary aim was to determine if the respiratory, cardiovascular and metabolic responses to exercise differ in survivors of preterm birth compared to term-born controls. Secondary aims were to determine if these exercise responses are impacted by BPD, changes in neonatal practice (*i.e.* pre- or post-surfactant era, represented by year of birth) or increasing age. Finally, we aimed to investigate if exercise test modality (cycle ergometer or treadmill) influenced exercise outcomes in those born preterm compared to term.

Methods

Search strategy and selection criteria

In the first of these back-to-back publications, Gibbons *et al.* [5] outline the systematic review search strategy, selection criteria, data collection, extraction, synthesis, analysis of study quality and selection bias in detail (PROSPERO: CRD42022320775). Briefly, searches were designed to capture studies investigating CPET outcomes, in addition to static lung volumes, gas transfer and oscillometry, in preterm-born populations compared with term-born controls. CPET outcomes were chosen and categorised to reflect the overall aerobic capacity (peak $\dot{V}_{O_2}$, $\dot{V}_{O_2}$ to work rate (WR) slope), metabolic (respiratory exchange ratio (RER)), pulmonary gas exchange efficiency (slopes of minute ventilation ($\dot{V}_E$) *versus* carbon dioxide production ($\dot{V}_{CO_2}$) and oxygen consumption ($\dot{V}_{O_2}$)), ventilatory ($\dot{V}_E$, breathing frequency (f_b), tidal volume (V_T), exercise flow limitation) and cardiovascular (heart rate (HR), oxygen pulse (represented by $\dot{V}_{O_2}$/HR)) responses to exercise. Systematic review searches were carried out on 29 April 2022 and updated on 29 November 2024. During data extraction, two additional outcomes were frequently reported, and were thus added to the analysis *post hoc*: peak WR to reflect maximal functional capacity and the $\dot{V}_{O_2}$ at anaerobic threshold (AT).

Studies were eligible for inclusion in this meta-analysis if 1) they reported CPET outcomes for both cohorts with a history of preterm birth (with and/or without a history of BPD) and cohorts who were born at term; 2) CPET was performed using a cycle ergometer or treadmill with direct, metabolic measurement of end-tidal gas; and 3) they had data that were reported as mean±SD or were appropriate for transformation to mean±SD using methods previously outlined [4]. Studies were excluded if they performed exercise testing with indirect estimates of $\dot{V}_{O_2}$. Where data from the same cohort spanned multiple publications, only the study with the most complete data set was included. For CPET outcomes expressed in multiple formats, a single format was extracted for analysis, with preference given to % predicted values, then to

body weight relative values (*e.g.* $\dot{V}_{O_2}$ in $mL \cdot min^{-1} \cdot kg^{-1}$) and lastly to absolute values (*e.g.* $\dot{V}_{O_2}$ in $L \cdot min^{-1}$). AT data were included when studies used the "V-slope" or "ventilatory equivalents" methods to determine AT [22]. Gas exchange efficiency was defined as the regression slope of $\dot{V}_E$ against $\dot{V}_{CO_2}$ (represented by $\dot{V}_E/\dot{V}_{CO_2}$ slope) [23].

Data analysis

Meta-analyses were performed in R (version 4.3.2; www.r-project.org) using the *meta* [24], *metafor* [25] and *dmetar* packages [26]. Briefly, the standardised mean difference (SMD) between pooled term-born and preterm-born groups for each study and for each CPET outcome was calculated. The SMD represents the mean difference between two groups relative to a pooled SD of those groups, and allows comparison across multiple studies when outcomes are expressed in differing formats (*e.g.* $L \cdot min^{-1}$, $mL \cdot min^{-1} \cdot kg^{-1}$ or % predicted) [27]. Meta-analyses were conducted to determine the overall SMD for each outcome. Random-effects models were used owing to expected high levels of heterogeneity, and Hedges' *g* correction was applied to account for studies with small sample sizes. Heterogeneity (I^2) was calculated using the restricted-maximum likelihood method (as recommended for continuous outcome data [28]) with Knapp–Hartung adjustments to control for uncertainty in between-study heterogeneity. To address the secondary aims, meta-analyses were repeated with preterm groups sub-categorised by BPD status, according to the study's reported definitions of BPD. Additionally, meta-regression analyses were used to investigate the impact of age and changes in neonatal care over time by plotting the SMD of each CPET outcome against the mean age and birth year of the cohorts. Meta-regression analysis required at least 10 cohorts per moderator to avoid over-fitting of regression models [29], and significance was determined by F-tests. Statistical significance was set at $p \leqslant 0.05$. Subgroup analyses were conducted using Q-tests to assess the impact of exercise modality (cycle ergometer or treadmill) on the differences between the preterm and term groups for each outcome. Q-tests assess if differences in subgroups are more likely due to sampling error or true differences in the effect size between subgroups [27]. Full details of the data analysis techniques are described in Gibbons *et al.* [5].

Risk of bias was assessed using a modified version of the Newcastle-Ottawa Quality Assessment Scale [30]. Based on this scale, each study was given a rating of low, medium or high risk of bias based on Agency of Healthcare Research and Quality Standards. Subgroup analysis was performed to compare if studies rated as low risk of bias differed significantly from those rated as medium or high risk of bias. Publication bias was assessed visually using funnel plots, and objectively with Egger's test when the outcome was reported in 10 or more studies [31].

Results

Study characteristics

The systematic review study selection and exclusions are summarised in figure 1. Detailed characteristics for all CPET studies included in the systematic review are provided in supplement 1: table E1 and the backing article's supplemental material (supplement 2: table E2 of Gibbons *et al.* 2025 [5]). From the systematic review, there were 124 studies identified containing CPET data across 48 unique cohorts, 47 of which were included in this meta-analysis [13, 17, 18, 21, 32–74]. All extracted and pooled data are tabulated in supplement 1: table E2. These studies resulted in 2149 preterm-born participants and 1650 term-born controls included in the analyses. Of the preterm group, 564 participants had a neonatal diagnosis of BPD and 638 were preterm without a diagnosis of BPD. The BPD status of the remaining 947 participants was not reported. CPET was performed on a treadmill in 15 studies, by cycle ergometry in 31 studies and by both in one study [54]. Median cohort age varied from 7 to 28 years of age, and the birth year of the cohorts ranged from 1973 to 2014.

Study quality, publication bias and risk of bias

Study quality varied substantially across studies, with the risk of bias rated low for 36 studies, medium for five studies and high for six studies (supplement 1: table E3). Similarly, between-study heterogeneity (I^2) varied across outcomes, ranging from 29% for the minute ventilation *versus* CO_2 production slope ($\dot{V}_E/\dot{V}_{CO_2}$ slope), to 75% for peak RER. Publication bias was evident (*via* asymmetrical funnel plots and significant Egger's test) when comparing the preterm group to the term group for the peak tidal volume variable. However, once the groups were separated by BPD status, Egger's test no longer reached statistical significance (supplement 2), implying that the heterogeneity in the combined preterm group may result from differences in disease state between the BPD and No BPD groups. Risk of bias subgroups analysis (supplement 1: table E4) revealed that studies rated to have medium-to-high risk of bias demonstrated a larger difference (SMD) in HR between the preterm and term groups.

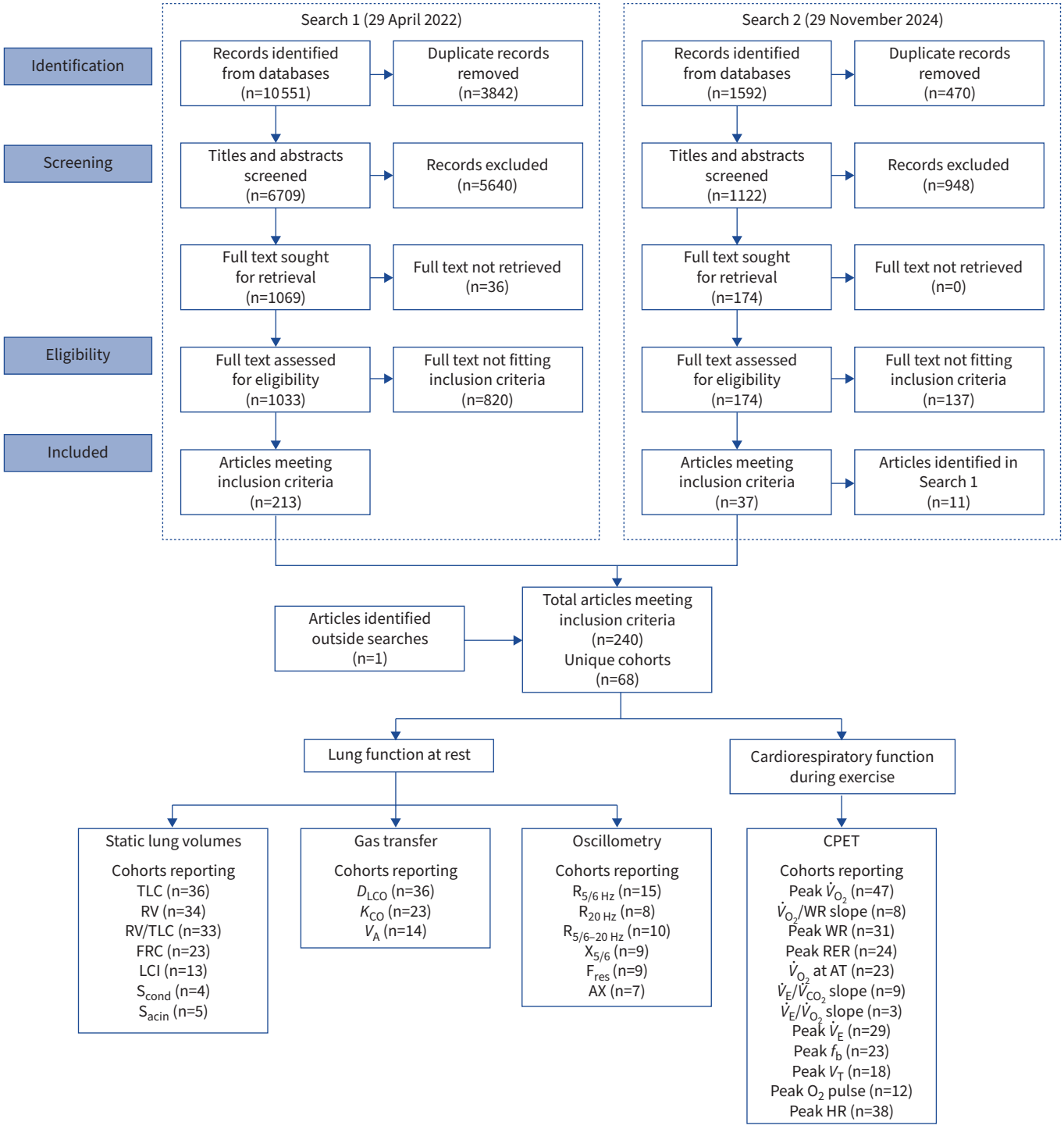

FIGURE 1 Study selection flowchart. Cardiorespiratory function during exercise (bottom right). TLC: total lung capacity; RV: residual volume; FRC: functional residual capacity; LCI: lung clearance index; S_{cond}: conductive ventilation heterogeneity; S_{acin}: acinar ventilation heterogeneity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; K_{CO}: transfer coefficient for carbon monoxide; V_A: alveolar volume; $R_{5/6\ Hz}$: airway resistance at 5/6 Hz; $R_{5/6–20\ Hz}$: difference between airway resistance at 5/6 Hz and 20 Hz; F_{res}: resonant frequency; AX: reactance area; $\dot{V}_{O_2}$: oxygen consumption; WR: work rate; $\dot{V}_{O_2}$/WR slope: $\dot{V}_{O_2}$ *versus* work rate slope; RER: respiratory exchange ratio; AT: aerobic threshold; $\dot{V}_E/\dot{V}_{CO_2}$ slope: minute ventilation *versus* carbon dioxide production slope; $\dot{V}_E/\dot{V}_{O_2}$ slope: minute ventilation *versus* oxygen consumption slope; $\dot{V}_E$: minute ventilation; f_b: breathing frequency; V_T: tidal volume; O_2 pulse: oxygen pulse ($\dot{V}_{O_2}$/HR); HR: heart rate.

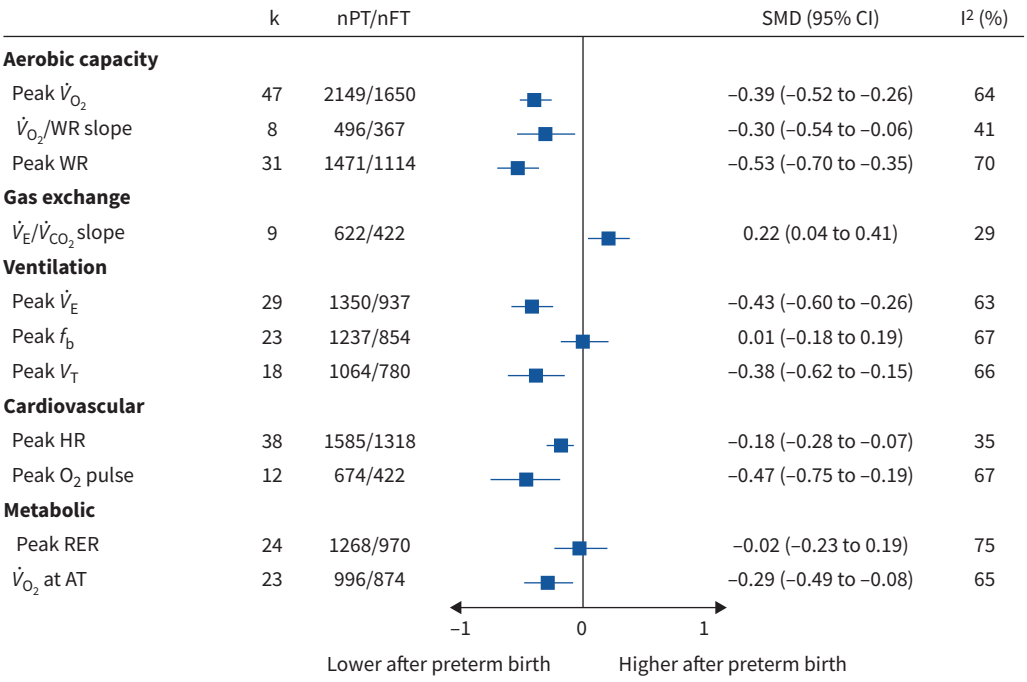

FIGURE 2 Meta-analyses of cardiopulmonary exercise testing (CPET) outcomes for preterm-born participants compared with term-born controls. k: number of cohorts; nPT: number of preterm individuals in analysis; nFT: number of full-term controls in analysis; SMD: standardised mean difference; 95% CI: 95% confidence interval; $\dot{V}_{O_2}$: oxygen consumption; $\dot{V}_{O_2}$/WR slope: $\dot{V}_{O_2}$ *versus* work rate slope; WR: work rate; $\dot{V}_E/\dot{V}_{CO_2}$ slope: minute ventilation *versus* CO_2 production slope; $\dot{V}_E$: minute ventilation; f_b: breathing frequency; V_T: tidal volume; HR: heart rate; O_2 pulse: oxygen pulse ($\dot{V}_{O_2}$/HR); RER: respiratory exchange ratio; AT: anaerobic threshold.

Meta-analysis

A summary of the primary meta-analysis results, including the number of studies reporting each CPET outcome, is presented in figure 2, with differences between the preterm and term groups expressed as SMD with 95% confidence intervals (95% CIs). Forest plots for all CPET outcomes in this meta-analysis, including details on the reported measurement units for each study, are provided in supplement 3. The analysis of peak $\dot{V}_{O_2}$ from 47 studies further evidenced that those born preterm (n=2149) had impaired aerobic capacity (peak $\dot{V}_{O_2}$) compared with term-born (n=1650) controls (SMD −0.39, 95% CI −0.52 to −0.26, k=47). The WR at peak exercise was also lower in the preterm group (SMD −0.53, 95% CI −0.70 to −0.35, k=31), as was the $\dot{V}_{O_2}$/WR slope (SMD −0.30, 95% CI −0.54 to −0.06, k=8).

Respiratory: gas exchange

Gas exchange efficiency was impaired in the preterm-born group, as represented by elevated $\dot{V}_E/\dot{V}_{CO_2}$ slopes (SMD 0.22, 95% CI 0.04 to 0.41, k=9) compared to the term-born group.

Respiratory: ventilation

Impaired ventilatory indices at peak exercise were identified in those born preterm compared to term-born counterparts. $\dot{V}_E$ at peak exercise was lower in the preterm group (SMD −0.43, 95% CI −0.60 to −0.26, k=29) with reduced V_T at peak exercise compared to the term group (SMD −0.38, 95% CI −0.62 to −0.15, k=18). Breathing frequency at peak exercise was not different between the preterm and term groups (SMD 0.01, 95% CI −0.18 to 0.19, k=23).

Cardiovascular

Impaired cardiovascular indices were also observed in the preterm group with both HR and O_2 pulse reduced at peak exercise compared to term-born controls (HR: SMD −0.18, 95% CI −0.28 to −0.07, k=38; O_2 pulse: SMD −0.47, 95% CI −0.75 to −0.19, k=12).

TABLE 1 Repeated meta-analyses for BPD *versus* Term and No BPD *versus* Term groups

	BPD *versus* Term			No BPD *versus* Term		
	k (nPT/nFT)	SMD (95% CI)	I^2 (%)	k (nPT/nFT)	SMD (95% CI)	I^2 (%)
Aerobic capacity						
Peak $\dot{V}_{O_2}$	24 (564/794)	**−0.51 (−0.73 to −0.29)**	63	21 (638/682)	**−0.38 (−0.59 to −0.17)**	56
$\dot{V}_{O_2}$/WR slope	4 (99/203)	−0.45 (−1.09 to 0.20)	51	4 (237/203)	−0.37 (−1.07 to 0.33)	64
Peak WR	16 (390/638)	**−0.66 (−0.92 to −0.41)**	59	15 (520/559)	**−0.32 (−0.60 to −0.03)**	69
Gas exchange						
$\dot{V}_E/\dot{V}_{CO_2}$ slope	5 (140/266)	0.23 (−0.19 to 0.66)	46	5 (279/223)	**0.22 (0.03 to 0.41)**	0
Ventilation						
Peak $\dot{V}_E$	18 (430/542)	**−0.53 (−0.74 to −0.32)**	48	14 (428/387)	−0.25 (−0.51 to 0.02)	48
Peak f_b	11 (272/408)	0.15 (−0.06 to 0.36)	22	10 (396/347)	−0.08 (−0.29 to 0.12)	21
Peak V_T	13 (398/584)	**−0.57 (−0.78 to −0.37)**	46	10 (415/462)	**−0.13 (−0.24 to −0.02)**	0
Cardiovascular						
Peak HR	19 (432/590)	**−0.37 (−0.55 to −0.19)**	31	18 (444/542)	−0.18 (−0.35 to 0.00)	29
Peak O_2 pulse	8 (203/270)	**−0.63 (−0.85 to −0.42)**	0	7 (315/229)	−0.47 (−1.03 to 0.10)	75
Metabolic						
Peak RER	13 (326/420)	−0.18 (−0.43 to 0.07)	47	13 (459/392)	−0.10 (−0.38 to 0.18)	57
$\dot{V}_{O_2}$ at AT	11 (284/372)	−0.18 (−0.50 to 0.15)	60	8 (346/296)	−0.33 (−0.76 to 0.11)	68

Bold text indicates significant outcomes ($p \leqslant 0.05$). BPD: bronchopulmonary dysplasia; k: number of cohorts; nPT: number of preterm participants; nFT: number of full-term control participants; SMD: standardised mean difference; 95% CI: 95% confidence interval; I^2: between-study heterogeneity; $\dot{V}_{O_2}$: oxygen consumption; $\dot{V}_{O_2}$/WR slope: $\dot{V}_{O_2}$ *versus* work rate slope; WR: work rate; $\dot{V}_E/\dot{V}_{CO_2}$ slope: minute ventilation *versus* CO_2 production slope; $\dot{V}_E$: minute ventilation; f_b: breathing frequency; V_T: tidal volume; HR: heart rate; O_2 pulse: oxygen pulse ($\dot{V}_{O_2}$/HR); RER: respiratory exchange ratio; AT: anaerobic threshold.

Metabolic

Metabolic indices showed no difference in the RER at peak exercise between the preterm-born and term-born groups (SMD −0.02, 95% CI −0.23 to 0.19, k=24). However, the $\dot{V}_{O_2}$ at AT was lower in the preterm group compared to the term group (SMD −0.29, 95% CI −0.49 to −0.08, k=23).

Preterm birth with and without BPD

Table 1 shows the SMD (95% CI) for each CPET outcome grouped by the presence or absence of a neonatal diagnosis of BPD. These data suggest that the group with BPD may have greater respiratory deficits during exercise, relative to term-born controls, than the preterm group without BPD.

Meta-regression

Meta-regression analyses (figure 3) showed that the aerobic capacity of the preterm group diverged further from the term group with increasing age. Peak $\dot{V}_{O_2}$, peak WR and $\dot{V}_{O_2}$ at AT all deviated further from the term group with increasing age, shifting by 0.02 (p=0.04), 0.03 (p=0.03) and 0.03 (p=0.01) SMD units per year away from the term-born population, respectively. Birth year was associated with a minor improvement in HR at peak exercise, shifting by 0.01 (p=0.03) SMD units per birth year towards the term-born population. No further associations between CPET outcomes and birth year or age at CPET were observed (supplement 1: table E5).

Exercise modality

Subgroup analyses (table 2) revealed that the SMDs between preterm- and term-born groups were similar for peak $\dot{V}_{O_2}$ on both cycle ergometry and treadmill tests (SMD −0.4, 95% CI −0.56 to −0.24, k=31 *versus* SMD −0.4, 95% CI −0.65 to −0.14, k=15). However, the preterm group were more likely to have a lower peak HR (compared with term-born peers) with treadmill tests (SMD −0.25, 95% CI −0.40 to −0.10, k=13) compared to cycle ergometry tests (SMD −0.12, 95% CI −0.25 to 0.01, k=22). No further differences with exercise modality were observed.

Discussion

Our findings demonstrate that preterm birth is associated with reduced exercise capacity (peak $\dot{V}_{O_2}$, $\dot{V}_{O_2}$ at AT and peak WR), which may diverge further from the term-born population with advancing age. Additionally, we consolidated the published literature on exercise outcomes beyond peak $\dot{V}_{O_2}$ for the first time in survivors of preterm birth. In doing so, we report impairment in all physiological domains of exercise capacity assessed by CPET, including the ventilatory, gas exchange, cardiovascular and metabolic domains.

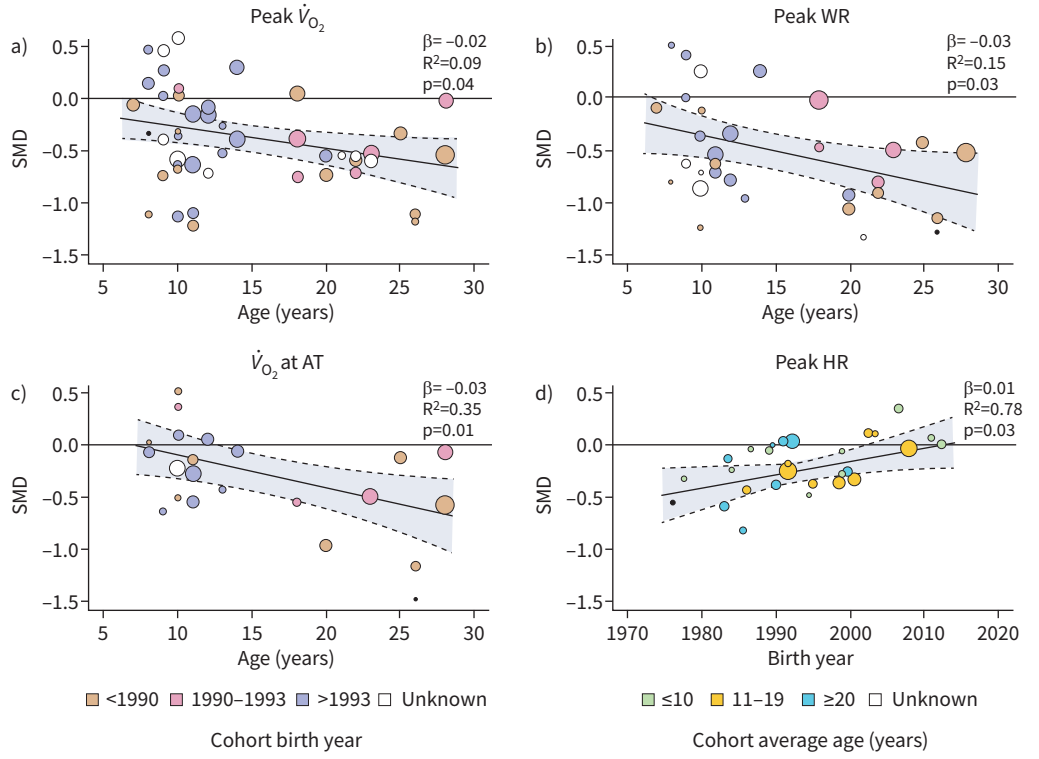

FIGURE 3 Panel of significant meta-regression results, with R^2 showing the heterogeneity accounted for by the moderator, and β, the regression coefficient. Significance (p) was tested using an F-test. $\dot{V}_{O_2}$: oxygen consumption; WR: work rate; AT: anaerobic threshold; HR: heart rate; SMD: standardised mean difference.

Reduced peak $\dot{V}_{O_2}$ has been previously reported in systematic reviews of (largely) children born preterm [11], and adults born preterm with very low birthweight [12]. The former study concluded that the small reductions observed in peak $\dot{V}_{O_2}$ (in the predominantly paediatric population) were unlikely to be of clinical significance [11]. However, larger differences were reported in the meta-analysis of adult peak $\dot{V}_{O_2}$ [12]. Our lifespan analysis suggests that age-related worsening may be a factor; however, longitudinal studies are needed to address this hypothesis, which are scarce. To date, only two small Norwegian cohorts have investigated changes in exercise capacity over time in a preterm population, one studying changes from childhood to adolescence [39], and the second from adolescence to adulthood [38]. Both studies reported a lower peak $\dot{V}_{O_2}$ at the first assessment that persisted at follow-up; however, confidence intervals were wide, likely due to small sample sizes. Understanding how exercise capacity evolves across the lifespan may further our understanding of why those born preterm are at an elevated risk of morbidity and mortality, decades after preterm birth.

This meta-analysis revealed reduced $\dot{V}_E$ and V_T at peak exercise, indicating an impaired respiratory response to exercise. This finding may be due to anthropometric differences; preterm-born individuals are generally shorter and lighter than their term-born counterparts [75] and $\dot{V}_E$ and V_T data are typically expressed in absolute units ($L \cdot min^{-1}$ and L, respectively), despite being size dependent. Alternatively, reduced V_T, in the presence of expiratory flow limitation, may be a compensatory mechanism to reduce work of breathing [59]. In a small cohort of extremely preterm-born adults (n=35), Lovering *et al.* [76] demonstrated that expiratory flow limitation is encountered even at low-intensity exercise, principally for those with a neonatal diagnosis of BPD. Others have also shown the increased rates of expiratory flow limitation during exercise in children born preterm [59, 62]. Unfortunately, meta-analysis of these data was not possible owing to the small number of studies reporting on expiratory flow limitation (n=3) and significant heterogeneity in the reporting of these results. Considered together, the reduced $\dot{V}_E$ and V_T during exercise reported herein, the increased prevalence of expiratory flow limitation [59, 76] and the high burden of exertional respiratory symptoms in this population [77] suggest that mechanical constraints to ventilation during exercise are likely for those born preterm.

TABLE 2 Bike *versus* treadmill subgroup-effects meta-analysis for preterm *versus* term group

	Cycle ergometry		Treadmill		Both		Total		Qb	p-value[#]
	k	SMD (95% CI)	k	SMD (95% CI)	k	SMD (95% CI)	k	SMD (95% CI)		
Aerobic capacity										
Peak $\dot{V}_{O_2}$	31	−0.4 (−0.56 to −0.24)	15	−0.4 (−0.65 to −0.14)	1	0.09 (−0.55 to 0.72)	47	−0.39 (−0.52 to −0.26)	2.13	0.34
Peak WR	21	−0.56 (−0.78 to −0.33)	10	−0.47 (−0.8 to −0.14)	NR		31	−0.53 (−0.70 to −0.35)	0.23	0.63
Gas exchange										
$\dot{V}_E/\dot{V}_{CO_2}$ slope	8	0.21 (0.01 to 0.41)	1	0.44 (−0.13 to 1.01)	NR		9	0.22 (0.04 to 0.41)	0.55	0.46
Ventilation										
Peak $\dot{V}_E$	20	−0.34 (−0.5 to −0.18)	8	−0.59 (−1.11 to −0.07)	1	−0.88 (−1.55 to −0.21)	29	−0.43 (−0.60 to −0.26)	3.4	0.18
Peak f_b	16	0.08 (−0.15 to 0.32)	6	−0.16 (−0.53 to 0.2)	1	−0.3 (−0.95 to 0.34)	23	0.01 (−0.18 to 0.19)	2.61	0.27
Peak V_T	14)	−0.4 (−0.74 to −0.07)	3	−0.31 (−1.08 to 0.46)	1	−0.8 (−1.47 to −0.14)	18	−0.38 (−0.62 to −0.15)	1.65	0.44
Cardiovascular										
Peak HR	24	**−0.12 (−0.25 to 0.01)**	13	**−0.25 (−0.4 to −0.1)**	1	−1.01 (−1.69 to −0.33)	38	−0.18 (−0.28 to −0.07)	7.74	**0.02**
Peak O_2 pulse	8	−0.59 (−0.92 to −0.26)	3	−0.17 (−1.57 to 1.23)	1	−0.22 (−0.86 to 0.42)	12	−0.47 (−0.75 to −0.19)	2.14	0.34
Metabolic										
Peak RER	18	0.07 (−0.17 to 0.32)	6	−0.31 (−0.73 to 0.11)	NR		24	−0.02 (−0.23 to 0.19)	3.65	0.06
$\dot{V}_{O_2}$ at AT	14	−0.35 (−0.62 to −0.08)	8	−0.24 (−0.63 to 0.15)	1	0.36 (−0.28 to 1.01)	23	−0.29 (−0.49 to −0.08)	4.16	0.12

Qb: heterogeneity between subgroups; k: number of cohorts; SMD: standardised mean difference; 95% CI: 95% confidence interval; $\dot{V}_{O_2}$: oxygen consumption; WR: work rate; $\dot{V}_E/\dot{V}_{CO_2}$ slope: minute ventilation *versus* CO_2 production slope; $\dot{V}_E$: minute ventilation; f_b: breathing frequency; V_T: tidal volume; HR: heart rate; O_2 pulse: oxygen pulse ($\dot{V}_{O_2}$/HR); RER: respiratory exchange ratio; AT: anaerobic threshold; NR: not reported. [#]: p-value reflects the significance (set at $p \leqslant 0.05$) of the differences in SMD between cycle ergometry and treadmill cardiopulmonary exercise testing outcomes, with bold text indicating significantly different outcomes.

In addition to ventilatory deficits, altered gas exchange can lead to respiratory limitation and symptoms on exercise. Efficient gas exchange relies on healthy pulmonary microvasculature and appropriate alveolar surface area, alterations in both of which have been implicated in the pathophysiology of BPD [4]. Gas exchange efficiency is represented by the minute ventilation for a given rate of CO_2 production ($\dot{V}_E/\dot{V}_{CO_2}$ slope). An elevated $\dot{V}_E/\dot{V}_{CO_2}$ slope indicates the respiratory system is less efficient at ventilating CO_2 out of the body during exercise. Studies included in this analysis reported the $\dot{V}_E/\dot{V}_{CO_2}$ slope. However, the $\dot{V}_E/\dot{V}_{CO_2}$ nadir may also be valuable in helping to understand ventilatory efficiency during exercise in this population [78]. This meta-analysis showed elevated $\dot{V}_E/\dot{V}_{CO_2}$ slopes on exercise in the preterm-born group, an outcome which has been implicated in a number of other disease pathologies with gas exchange abnormalities, such as COPD [79], heart failure [80] and pulmonary hypertension [81]. While the elevation in $\dot{V}_E/\dot{V}_{CO_2}$ slope in our analysis is modest, the chronic effects of subclinical impairments in gas exchange on exercise are not known for this population, and further investigation in this domain is warranted.

Our results suggest that survivors of preterm birth may (relative to term-born controls) have reduced cardiac output, with reductions in HR and stroke volume at peak exercise. While stroke volume is approximated from O_2 pulse in CPET, there is evidence supporting reduced stroke volume at peak exercise using direct measures in preterm-born cohorts (*e.g.* cardiac magnetic resonance imaging [82] or thoracic bioimpedance [17]). Nonetheless, it remains unknown whether reduced stroke volume is a consequence of smaller cardiac chamber size or myocardial dysfunction in those born preterm [83], and whether deficits progress over the life course. However, a recent Swedish registry study identified a 17-fold increased risk of incident heart failure among children and young adults born extremely preterm [84], and these CPET measures may help to identify preterm-born individuals at risk of early cardiovascular morbidity.

We showed that preterm-born individuals have a lower AT than term-born controls, with meta-regression analysis suggesting further decrements in AT with increasing age. Reduced AT indicates a switch to anaerobic metabolism at lower relative exercise intensities, and can result from impaired oxygen uptake, mitochondrial oxygen extraction or cardiac output (which may be a result of deconditioning) [22]. Elevated basal and stress-related mitochondrial oxygen consumption rates [6] and reduced mitochondrial density [85] have been reported in preterm-born adults and adolescents, which could explain their earlier attainment of AT during CPET. Similarly, altered body composition in preterm-born individuals, and particularly unfavourable fat distribution, could imply increased sedentary behaviours that would precipitate physical deconditioning [86]. Indeed, adolescent and adult survivors of preterm birth participate less in physical activity [87], which may result from a combination of neurodevelopmental, musculoskeletal and psychosocial factors [88, 89]. The consequences of reduced AT predispose this population to early-onset metabolic acidosis during exercise, and therefore a greater likelihood of fatiguing or developing respiratory symptoms on exercise, which may manifest as avoidance towards physical activity [89].

The interpretation of these data is limited by the fact that survivors of preterm birth are a heterogenous population with significantly varying geographical and neonatal characteristics [3], especially given the profound changes in perinatal care over the past three decades. Consequently, while we provide data separated for those with and without BPD (compared to term-born controls), all analyses have been conducted across the entire preterm population because we now understand that many individuals without BPD go on to develop prematurity-associated lung disease [90]. While a strength of this study is using SMD to pool CPET data expressed in different formats (% predicted, body weight corrected, raw data) to maximise the number of studies included, we need to interpret the findings with the knowledge that preterm-born people are sometimes of smaller stature than their age-equivalent peers [91]. In this meta-analysis, two studies reported outcomes as raw values for $\dot{V}_{O_2}$ [47, 74], which may widen the difference between the term and preterm groups. Others have argued that a per kg adjustment may not be an adequate adjustment for body size [92]. Regardless, expressing CPET outcomes such as $\dot{V}_{O_2}$ peak relative to body weight is the most universally used way to account for body size differences. Adding to this, differences in exercise testing protocols, technology, methodology and cohort inclusion/exclusion criteria across different studies have likely contributed to the high heterogeneity seen in our analyses. Furthermore, we excluded studies without a term-born control group, and for study cohorts with data published across multiple publications, only the study with the most comprehensive data was included. While this approach resulted in several studies being excluded, it does provide confidence in the differences reported between the preterm- and term-born populations.

In summary, this meta-analysis is the first to comprehensively report on deficits in respiratory, cardiovascular and metabolic measures at peak exercise in survivors of preterm birth. In our systematic review, no studies were identified that examined exercise capacity in cohorts born preterm after 30 years of age. This leaves a significant blind spot, inhibiting our understanding of the lifelong consequences of

preterm birth on exercise capacity. Moving forward, longitudinal studies in this growing population are needed to help elucidate the mechanisms and trajectories of exercise intolerance. Moreover, participation in physical activity and exercise across the lifespan should be encouraged to improve the physiological deficits in this population.

Provenance: Submitted article, peer reviewed.

Author contributions: M.L. Beaven contributed to the study search strategy, outcome selection, screening, data extraction, data validation, data analysis, data interpretation and manuscript preparation. J.T.D. Gibbons executed the study searches, conducted the formal data analysis, and contributed to the study design, search strategy, screening, database management, data extraction, data validation and review of the original draft. C.W. Course contributed to the study search strategy, screening, data validation and manuscript review. S.J. Kotecha contributed to the study outcome selection, search strategy, screening, data validation and data interpretation. T. Hixson and M. Zuidersma contributed to the study screening. A. Maiorana contributed to the study outcome selection, data interpretation and manuscript review. S. Kotecha contributed to the study outcome selection, search strategy and data interpretation. E.F. Smith contributed to the study outcome selection, data extraction, data validation, data analysis, data interpretation and manuscript review. S.J. Simpson contributed to the study outcome selection, search strategy, screening, data analysis, data interpretation and manuscript review. All authors contributed to the article and approved the submitted version.

Conflict of interest: E.F. Smith reports a leadership or fiduciary role as Board Director of Australian and New Zealand Society of Respiratory Science (unpaid role). The remaining authors have no conflicts to declare.

References

1 Simpson SJ, Turkovic L, Wilson AC, *et al.* Lung function trajectories throughout childhood in survivors of very preterm birth: a longitudinal cohort study. *Lancet Child Adolesc Health* 2018; 2: 350–359.
2 Simpson SJ, Du Berry C, Evans DJ, *et al.* Unravelling the respiratory health path across the lifespan for survivors of preterm birth. *Lancet Respir Med* 2024; 2: 167–180.
3 Kotecha SJ, Gibbons JTD, Course CW, *et al.* Geographical differences and temporal improvements in forced expiratory volume in 1 s of preterm-born children: a systematic review and meta-analysis. *JAMA Pediatr* 2022; 176: 867–877.
4 Gibbons JTD, Course CW, Evans EE, *et al.* Increasing airway obstruction through life following bronchopulmonary dysplasia: a meta-analysis. *ERJ Open Res* 2023; 9: 00046-2023.
5 Gibbons JTD, Beaven ML, Course CW, *et al*. Lung volumes, gas transfer and oscillimetry after preterm birth: systematic review and meta-analysis. *Eur Respir Rev* 2025; 34: 240151.
6 Kumari S, Barton GP, Goss KN. Increased mitochondrial oxygen consumption in adult survivors of preterm birth. *Pediatr Res* 2021; 90: 1147–1152.
7 Crump C. An overview of adult health outcomes after preterm birth. *Early Hum Dev* 2020; 150: 105187.
8 Kumar VHS. Cardiovascular morbidities in adults born preterm: getting to the heart of the matter! *Children (Basel)* 2022; 9: 1843.
9 World Health Organization. WHO Guidelines on Physical Activity and Sedentary Behaviour. Geneva, World Health Organization, 2020.
10 Crump C, Sundquist J, Winkleby MA, *et al.* Gestational age at birth and mortality from infancy into mid-adulthood: a national cohort study. *Lancet Child Adolesc Health* 2019; 3: 408–417.
11 Edwards MO, Kotecha SJ, Lowe J, *et al.* Effect of preterm birth on exercise capacity: a systematic review and meta-analysis. *Pediatr Pulmonol* 2015; 50: 293–301.
12 Poole G, Harris C, Greenough A. Exercise capacity in very low birth weight adults: a systematic review and meta-analysis. *Children (Basel)* 2023; 10: 1427.
13 Weigelt A, Bleck S, Huebner MJ, *et al.* Impact of premature birth on cardiopulmonary function in later life. *Eur J Pediatr* 2023; 182: 3265–3274.
14 Lovering AT, Duke JW. Reduced aerobic exercise capacity in adults born at very low birth weight: no small matter! *Am J Respir Crit Care Med* 2022; 205: 8–10.
15 Duke JW, Lewandowski AJ, Abman SH, *et al.* Physiological aspects of cardiopulmonary dysanapsis on exercise in adults born preterm. *J Physiol* 2022; 600: 463–482.
16 O'Dea CA, Logie K, Wilson AC, *et al.* Lung abnormalities do not influence aerobic capacity in school children born preterm. *Eur J Appl Physiol* 2021; 121: 489–498.
17 Haraldsdottir K, Watson AM, Pegelow DF, *et al.* Blunted cardiac output response to exercise in adolescents born preterm. *Eur J Appl Physiol* 2020; 120: 2547–2554.
18 Huckstep OJ, Burchert H, Williamson W, *et al.* Impaired myocardial reserve underlies reduced exercise capacity and heart rate recovery in preterm-born young adults. *Eur Heart J Cardiovasc Imaging* 2021; 22: 572–580.

19 Lewandowski AJ. Acute and chronic cardiac adaptations in adults born preterm. *Exp Physiol* 2022; 107: 405–409.
20 Lowe J, Hart K, Cousins M, *et al.* Ventilatory efficiency during exercise: data from a contemporary cohort of preterm-born children. *Eur Respir J* 2018; 52: Suppl. 62, PA557.
21 Yang J, Epton MJ, Harris SL, *et al.* Reduced exercise capacity in adults born at very low birth weight: a population-based cohort study. *Am J Respir Crit Care Med* 2022; 205: 88–98.
22 Sietsema KE, Sue DY, Stringer WW, *et al.* Wasserman & Whipp's Principles of Exercise Testing and Interpretation, 6th Edn. Philadelphia, PA, Wolters Kluwer, 2021.
23 Phillips DB, Collins S, Stickland MK. Measurement and interpretation of exercise ventilatory efficiency. *Front Physiol* 2020; 11: 659.
24 Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. *Evid Based Mental Health* 2019; 22: 153–160.
25 Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Softw* 2010; 36: 1–48.
26 Harrer M, Cuijpers P, Furukawa T, *et al.* dmetar: Companion R Package for the Guide 'Doing Meta-Analysis in R. 2019. Available from: https://dmetar.protectlab.org/
27 Harrer M, Cuijpers P, Furukawa TA, *et al.* Doing Meta-Analysis With R: a Hands-On Guide. 1st edn. Boca Raton, FL, Chapman & Hall/CRC Press, 2021.
28 Higgins J, Thomas J, Chandler J, *et al.* Cochrane Handbook for Systematic Reviews of Interventions version 6.3. London, Cochrane, 2022. Available from: https://training.cochrane.org/handbook
29 Deeks J, Higgins J, Altman DG. Analysing data and undertaking meta-analyses. *In:* Higgins JPT, Thomas J, Chandler J, *et al.*, eds. Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). London, Cochrane, 2023.
30 Wells GA, Shea B, O'Connell D, *et al.* The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. www.ohri.ca/programs/clinical_epidemiology/oxford.asp Date last updated: 3 May 2021.
31 Sterne JAC, Sutton AJ, Ioannidis JPA, *et al.* Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011; 343: d4002.
32 Abreu L, Costa-Rangel R, Gastaldi A, *et al.* Cardiorespiratory capacity assessment on children with bronchopulmonary dysplasia. *Braz Jo Phys Ther* 2007; 11: 105–111.
33 Bader D, Ramos AD, Lew CD, *et al.* Childhood sequelae of infant lung disease: exercise and pulmonary function abnormalities after bronchopulmonary dysplasia. *J Pediatr* 1987; 110: 693–699.
34 Baraldi E, Zanconato S, Zorzi C, *et al.* Exercise performance in very low birth weight children at the age of 7–12 years. *Eur J Pediatr* 1991; 150: 713–716.
35 Barker M, Merz U, Hertl MS, *et al.* School-age lung function and exercise capacity in former very low birth weight infants. *Pediatr Exerc Sci* 2003; 15: 44–55.
36 Burchert H, Lapidaire W, Williamson W, *et al.* aerobic exercise training response in preterm-born young adults with elevated blood pressure and stage 1 hypertension: a randomized clinical trial. *Am J Respir Crit Care Med* 2023; 207: 1227–1236.
37 Caskey S, Gough A, Rowan S, *et al.* Structural and functional lung impairment in adult survivors of bronchopulmonary dysplasia. *Ann Am Thorac Soc* 2016; 13: 1262–1270.
38 Clemm HH, Vollsæter M, Røksund OD, *et al.* Exercise capacity after extremely preterm birth: development from adolescence to adulthood. *Ann Am Thorac Soc* 2014; 11: 537–545.
39 Clemm HH, Vollsæter M, Røksund OD, *et al.* Adolescents who were born extremely preterm demonstrate modest decreases in exercise capacity. *Acta Paediatr* 2015; 104: 1174–1181.
40 Cousins M, Hart K, Williams EM, *et al.* Impaired exercise outcomes with significant bronchodilator responsiveness in children with prematurity-associated obstructive lung disease. *Pediatr Pulmonol* 2022; 57: 2161–2171.
41 Debevec T, Pialoux V, Millet GP, *et al.* Exercise overrides blunted hypoxic ventilatory response in prematurely born men. *Front Physiol* 2019; 10: 437.
42 Delfrate J. Impact de la Prématurité et de la Dysplasie Broncho-Pulmonaire sur les Échanges Gazeux et la Fonction Cardio-Pulmonaire au Décours d'un Exercice Maximal Chez de Jeunes Adultes [Impact of Prematurity and Bronchopulmonary Dysplasia on Gas Exchange and Cardiopulmonary Function During Maximal Exercise in Young Adults] [Master's Thesis]. Montreal, Polytechnique Montréal, 2017. Available from: https://publications.polymtl.ca/2554/
43 Duke JW, Gladstone IM, Sheel AW, *et al.* Premature birth affects the degree of airway dysanapsis and mechanical ventilatory constraints. *Exp Physiol* 2018; 103: 261–275.
44 Engan M, Engeset MS, Sandvik L, *et al.* Left vocal cord paralysis, lung function and exercise capacity in young adults born extremely preterm with a history of neonatal patent ductus arteriosus surgery – a national cohort study. *Front Pediatr* 2022; 9: 780045.
45 Evensen KAI, Steinshamn S, Tjønna AE, *et al.* Effects of preterm birth and fetal growth retardation on cardiovascular risk factors in young adulthood. *Early Hum Dev* 2009; 85: 239–245.

46 Fouzas S, Nourloglou A, Vervenioti A, *et al.* Cardiopulmonary exercise performance of children born non-extremely preterm. *Children (Basel)* 2024; 11: 198.
47 Gibson A-MF, Cheong J, Roberts G, *et al.* Maximal exercise abnormalities in extremely preterm, extremely low birth weight survivors at 18 years compared to term, normal birth weight controls [Conference abstract]. *Respirology* 2012; 17: Suppl. 1, 79.
48 Haraldsdottir K, Watson AM, Beshish AG, *et al.* Heart rate recovery after maximal exercise is impaired in healthy young adults born preterm. *Eur J Appl Physiol* 2019; 119: 857–866.
49 Hebestreit H, Staschen B, Hebestreit A. Ventilatory threshold: a useful method to determine aerobic fitness in children? *Med Sci Sports Exerc* 2000; 32: 1964–1969.
50 Hochwald O, Bentur L, Haddad Y, *et al.* Cardiopulmonary exercise testing in childhood in late preterms: comparison to early preterms and term-born controls. *J Pers Med* 2022; 12: 1547.
51 Joshi S, Powell T, Watkins WJ, *et al.* Exercise-induced bronchoconstriction in school-aged children who had chronic lung disease in infancy. *J Pediatr* 2013; 162: 813–818.
52 Kaiser CR. Aerobic Fitness and the Renin Angiotensin System in Adolescents Born Preterm With Very Low Birth Weight [Master's Thesis]. Winston-Salem, NC, Wake Forest University, 2016. Available from: https://wakespace.lib.wfu.edu/bitstream/handle/10339/59313/Kaiser_wfu_0248M_10901.pdf
53 Kaplan E, Bar-Yishay E, Prais D, *et al.* Encouraging pulmonary outcome for surviving, neurologically intact, extremely premature infants in the postsurfactant era. *Chest* 2012; 142: 725–733.
54 Karila C, Saulnier JP, Elie C, *et al.* Hypoventilation alvéolaire à l'exercice chez des enfants avec dysplasie bronchopulmonaire [Exercise alveolar hypoventilation in long-term survivors of bronchopulmonary dysplasia]. *Rev Mal Respir* 2008; 25: 303–312.
55 Kilbride H, Dinakar C, Carver T, *et al.* Pulmonary function, oxygen consumption, and exhaled nitric oxide measures for extremely low birth weight, heavier preterm, and term children [Conference abstract]. *J Invest Med* 2012; 60: 239.
56 Kilbride HW, Gelatt MC, Sabath RJ. Pulmonary function and exercise capacity for ELBW survivors in preadolescence: effect of neonatal chronic lung disease. *J Pediatr* 2003; 143: 488–493.
57 Kouroukli E, Hatziagorou E, Sarafidis K, *et al.* Chronic lung disease of prematurity *vs* cystic fibrosis: exercise capacity and ventilation inhomogeneity. *Eur Respir J* 2020; 56: Suppl. 64, 1173.
58 Kriemler S, Keller H, Saigal S, *et al.* Aerobic and lung performance in premature children with and without chronic lung disease of prematurity. *Clin J Sport Med* 2005; 15: 349–355.
59 MacLean JE, DeHaan K, Fuhr D, *et al.* Altered breathing mechanics and ventilatory response during exercise in children born extremely preterm. *Thorax* 2016; 71: 1012–1019.
60 Murray S. Abnormal Restrictive Constraints on Ventilation and Breathlessness Do Not Contribute to Exercise Intolerance in Adult Survivors of Preterm Birth with Bronchopulmonary Dysplasia [Master's Thesis]. Montreal, McGill University, 2018.
61 Narang BJ, Manferdelli G, Kepic K, *et al.* Effects of pre-term birth on the cardio-respiratory responses to hypoxic exercise in children. *Life (Basel)* 2022; 12: 79.
62 O'Dea CA, Logie K, Maiorana A, *et al.* Increased prevalence of expiratory flow limitation during exercise in children with bronchopulmonary dysplasia. *ERJ Open Res* 2018; 4: 00048-2018.
63 Parat S, Moriette G, Delaperche MF, *et al.* Long-term pulmonary functional outcome of bronchopulmonary dysplasia and premature birth. *Pediatr Pulmonol* 1995; 20: 289–296.
64 Pianosi PT, Fisk M. Cardiopulmonary exercise performance in prematurely born children. *Pediatr Res* 2000; 47: 653–658.
65 Prenzel F, Vogel M, Siekmeyer W, *et al.* Exercise capacity in children with bronchopulmonary dysplasia at school age. *Respir Med* 2020; 171: 106102.
66 Rideau Batista Novais A, Matecki S, Jaussent A, *et al.* Hyperventilation during exercise in very low birth weight school-age children may implicate inspiratory muscle weakness. *J Pediatr* 2012; 160: 415–420.
67 Ruf K, Thomas W, Brunner M, *et al.* Diverging effects of premature birth and bronchopulmonary dysplasia on exercise capacity and physical activity – a case control study. *Respir Res* 2019; 20: 260.
68 Santuz P, Baraldi E, Zaramella P, *et al.* Factors limiting exercise performance in long-term survivors of bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 1995; 152: 1284–1289.
69 Steenhorst JJ, Helbing W, van Genuchten WJ, *et al.* Cardiac dysfunction during exercise in young adults with bronchopulmonary dysplasia. *ERJ Open Res* 2024; 10: 00501-2023.
70 Svien LR. Health-related fitness of seven-to 10-year-old children with histories of preterm birth. *Pediatr Phys Ther* 2003; 15: 74–83.
71 Tsopanoglou SP, Davidson J, Dourado VZ, *et al.* Aerobic capacity of preterm children with very low birth weight at school age and its associated factors. *Arch Bronconeumol* 2020; 56: 157–162.
72 Vrijlandt EJLE, Gerritsen J, Boezen HM, *et al.* Lung function and exercise capacity in young adults born prematurely. *Am J Respir Crit Care Med* 2006; 173: 890–896.
73 Vrijlandt EJLE, Reijneveld SA, Aris-Meijer JL, *et al.* Respiratory health in adolescents born moderately-late preterm in a community-based cohort. *J Pediatr* 2018; 203: 429–436.

74 Welsh L, Kirkby J, Lum S, *et al.* The EPICure study: maximal exercise and physical activity in school children born extremely preterm. *Thorax* 2010; 65: 165–172.

75 Jańczewska I, Wierzba J, Jańczewska A, *et al.* Prematurity and low birth weight and their impact on childhood growth patterns and the risk of long-term cardiovascular sequelae. *Children (Basel)* 2023; 10: 1599.

76 Lovering AT, Elliott JE, Laurie SS, *et al.* Ventilatory and sensory responses in adult survivors of preterm birth and bronchopulmonary dysplasia with reduced exercise capacity. *Ann Am Thorac Soc* 2014; 11: 1528–1537.

77 Neder JA, Berton DC, Marillier M, *et al.* Inspiratory constraints and ventilatory inefficiency are superior to breathing reserve in the assessment of exertional dyspnea in COPD. *COPD* 2019; 16: 174–181.

78 Neder JA, Berton DC, Rocha A, *et al.* Abnormal patterns of response to incremental CPET. *In*: Palange P, Laveneziana P, Neder A, Ward SA, eds. Clinical Exercise Testing (ERS Monograph). Sheffield, European Respiratory Society, 2018; pp. 34–58.

79 Neder JA, Berton DC, Arbex FF, *et al.* Physiological and clinical relevance of exercise ventilatory efficiency in COPD. *Eur Respir J* 2017; 49: 1602036.

80 Nayor M, Xanthakis V, Tanguay M, *et al.* Clinical and hemodynamic associations and prognostic implications of ventilatory efficiency in patients with preserved left ventricular systolic function. *Circ Heart Fail* 2020; 13: e006729.

81 Raza F, Dharmavaram N, Hess T, *et al.* Distinguishing exercise intolerance in early-stage pulmonary hypertension with invasive exercise hemodynamics: rest V_E/V_{CO2} and $ETCO_2$ identify pulmonary vascular disease. *Clin Cardiol* 2022; 45: 742–751.

82 Macdonald JA, Roberts GS, Corrado PA, *et al.* Exercise-induced irregular right heart flow dynamics in adolescents and young adults born preterm. *J Cardiovasc Magn Reson* 2021; 23: 116.

83 Goss KN, Haraldsdottir K, Beshish AG, *et al.* Association between preterm birth and arrested cardiac growth in adolescents and young adults. *JAMA Cardiol* 2020; 5: 910–919.

84 Carr HBS, Cnattingius SMDP, Granath FP, *et al.* Preterm birth and risk of heart failure up to early adulthood. *J Am Coll Cardiol* 2017; 69: 2634–2642.

85 Wood CL, Tinnion R, Hollingsworth KG, *et al.* Muscle function, body composition, insulin sensitivity and physical activity in adolescents born preterm: impact of gestation and vitamin D status. *Nutrients* 2022; 14: 5045.

86 Liao J, Hu M, Imm K, *et al.* Association of daily sitting time and leisure-time physical activity with body fat among U.S. adults. *J Sport Health Sci* 2022; 13: 195–203.

87 Francis IJ. Physical Activity and Aerobic Fitness in Adolescence and Blood Pressure in Young Adults Born Preterm with Very Low Birth Weight [Master's Thesis]. Winston-Salem, NC, Wake Forest University, 2021.

88 Lowe J, Cousins M, Kotecha SJ, *et al.* Physical activity outcomes following preterm birth. *Paediatr Respir Rev* 2017; 22: 76–82.

89 Tikanmäki M, Kaseva N, Tammelin T, *et al.* Leisure time physical activity in young adults born preterm. *J Pediatr* 2017; 189: 135–142.

90 Du Berry C, Nesci C, Cheong JLY, *et al.* Long-term expiratory airflow of infants born moderate-late preterm: a systematic review and meta-analysis. *eClinicalMedicine* 2022; 52: 101597.

91 Suikkanen J, Nurhonen M, Cole TJ, *et al.* Preterm birth and subsequent timing of pubertal growth, menarche, and voice break. *Pediatr Res* 2022; 92: 199–205.

92 Tanner JM. Fallacy of per-weight and per-surface area standards, and their relation to spurious correlation. *J Appl Physiol* 1949; 2: 1–15.