Physical activity level in children born extremely preterm: a comparison between children with and without bronchopulmonary dysplasia

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Abstract

Introduction: Children with a history of bronchopulmonary dysplasia (BPD) may have lower physical activity levels, but evidence to date is based on self-report. This study compared physical activity levels between children born extremely preterm with and without history of BPD, and examined their associations with pulmonary magnetic resonance imaging (MRI) and pulmonary function test (PFT) indices. **Methods:** This multi-centre cross-sectional study included children aged 7-9 years born extremely preterm, with and without BPD. Children wore a pedometer for one week, then completed the Physical Activity Questionnaire (PAQ), pulmonary MRI, and PFT. Spearman correlations and multivariable linear regression modelling were performed. **Results:** Of 45 children, 28 had a history of moderate-severe BPD. There were no differences in any physical activity outcomes by BPD status. Higher average daily step count and higher average daily moderate-vigorous physical activity (MVPA) were each correlated with greater forced vital capacity (r=0.41 and 0.58), greater MRI lung proton density at full expiration (r=0.42 and 0.49), and lower lung clearance index (r=-0.50 and -0.41). After adjusting for MRI total proton density and BPD status, a 5% increase in forced expiratory volume at one second was associated with 738 (95%CI: 208, 1268) more steps per day and 0.1 (0.0, 0.2) more hours of MVPA, respectively. **Conclusion:** School-aged children born extremely preterm have similar physical activity levels to their peers, regardless of history of BPD. MRI and PFT measures suggestive of gas trapping and/or airflow obstruction are associated with lower physical activity levels.

TITLE PAGE

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Consent to participate: Written informed consent and/or assent was obtained from all children and their parents included in this study.

Conflicts of interest: The authors have no relevant conflicts of interest to declare.

Author contribution statement: This study was conceptualized by Dr. Katz, and designed by Drs. Roeper, Chaput, Katz, Barrowman, and Momoli. Recruitment and acquisition of the respiratory symptom questionnaire, pulmonary function tests, and pedometer data was conducted by Drs. Katz, Luu, Nuyt, Thebaud, Moraes, Tse, Ben Fadel, and Roeper. Drs. Santyr, Abdeen, Deschenes, and Couch contributed to MRI data acquisition and interpretation. Dr. Parraga was responsible for the MRI data analysis and interpretation. Ms. Blinder was responsible for project management, data acquisition, and data validation.

Statistical analysis was performed by Ms. Hayawi, with oversight by Dr. Barrowman. Dr. Roeper wrote the initial manuscript draft. All authors contributed to data interpretation and revision of the manuscript, and approved the final version being submitted.

Keywords: physical activity, bronchopulmonary dysplasia, prematurity, magnetic resonance imaging, pediatric, pulmonary function test

Running head: Physical activity in children with and without BPD

SUMMARY/ABSTRACT

Introduction: Children with a history of bronchopulmonary dysplasia (BPD) may have lower physical activity levels, but evidence to date is based on self-report. This study compared physical activity levels between children born extremely preterm with and without history of BPD, and examined their associations with pulmonary magnetic resonance imaging (MRI) and pulmonary function test (PFT) indices.

Methods: This multi-centre cross-sectional study included children aged 7-9 years born extremely preterm, with and without BPD. Children wore a pedometer for one week, then completed the Physical Activity Questionnaire (PAQ), pulmonary MRI, and PFT. Spearman correlations and multivariable linear regression modelling were performed.

Results: Of 45 children, 28 had a history of moderate-severe BPD. There were no differences in any physical activity outcomes by BPD status. Higher average daily step count and higher average daily moderate-vigorous physical activity (MVPA) were each correlated with greater forced vital capacity (r=0.41 and 0.58), greater MRI lung proton density at full expiration (r=0.42 and 0.49), and lower lung clearance index (r=-0.50 and -0.41). After adjusting for MRI total proton density and BPD status, a 5% increase in forced expiratory volume at one second was associated with 738 (95%CI: 208, 1268) more steps per day and 0.1 (0.0, 0.2) more hours of MVPA, respectively.

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INTRODUCTION

In recent decades, there has been a significant reduction in mortality associated with premature birth, allowing for a greater number of survivors of extremely preterm birth[1]. Bronchopulmonary dysplasia (BPD; defined as a need for oxygen at or beyond 28 days of life, and characterized in severity by degree of support required at 36 weeks post-menstrual age)[2] is a common comorbidity in preterm neonates, associated with long-term effects on respiratory function[3,4]. As the survival of extremely preterm children increases, there is a need to evaluate the outcomes of these children in all aspects of life and health, and how different clinical and behavioural factors might mitigate morbidity. Participation in physical activity can impact the health and well-being of school-aged children[5], and engagement in physical activity in childhood increases the likelihood of ongoing physical activity in adulthood[6]. Evaluating and encouraging physical activity in preterm born children and youth is therefore important for improving long-term health outcomes.

Prior studies on the physical activity of children with BPD have demonstrated lower participation in physical activity through self-report[5,7,8]. Study findings have been mixed, showing both normal and reduced exercise tolerance[9,10]and similar aerobic capacity[7] in children born preterm (with and without BPD) when compared to children born at term. Children with BPD have been shown to have pulmonary function abnormalities including reduced forced expiratory volume in one second ($FEV1$)[7,8,11] and mid-expiratory flows (FEF_{25-75})[8], moderate-to-severe airflow obstruction and hyperinflation[9,11]. They may also have an increased respiratory rate[11], lower tidal volumes[11], and decreased peak oxygen saturation[9,11] during aerobic activity, compared to their full term peers without BPD. Furthermore, most adolescents and young adults who had BPD in infancy have some degree of pulmonary dysfunction (airway obstruction, hyper-reactivity, hyperinflation), even if

they were clinically asymptomatic[12]. Given these findings of reduced lung function and exercise capacity in children with BPD, it is important to understand physical activity in this population and its relationship to measures of lung disease.

To date, studies evaluating degree of participation in physical activity have been through self-report assessment tools, rather than by objective means. There may be important differences between perceived and actual participation in physical activity in this population, and physical activity may be mitigated by other clinical or behavioural factors. This study therefore sought to compare perceived exercise tolerance and objective physical activity data in a home environment in children born extremely preterm (<28 weeks gestation), who are now school-aged (7-9 years), with and without history of BPD. We also examined associations of physical activity with pulmonary magnetic resonance imaging (MRI) and lung function. Our hypothesis was that children with a history of BPD would have decreased physical activity compared to those without a history of BPD.

MATERIALS AND METHODS

Study design and setting

This study was performed in conjunction with the PICTURE study (Pulmonary Magnetic Resonance Imaging of Ex-preterm Children with and without Bronchopulmonary Dysplasia to Understand Risk of Emphysematous Changes; clinicaltrials.gov: NCT02921308)[13]. The PICTURE study is a multicentre, cross-sectional study which aimed to evaluate the use of ultra-short echo time MRI to assess lung structure in children born extremely preterm with and without BPD. This study was performed at three tertiary pediatric hospitals: the Children's Hospital of Eastern Ontario (Ottawa, Ontario), The Hospital for Sick Children (Toronto, Ontario), and the Centre Hospitalier Universitaire Sainte-Justine (Montreal, Quebec). Local research ethics board approval was obtained at each of the participating sites.

Participants

Children were identified from local neonatal follow-up databases at the respective study sites and consent/assent was obtained by the research coordinator. Children were eligible if they were 7-9 years of age and born at less than 28 weeks' gestation, with and without history of BPD, and were enrolled in the PICTURE study[13]. Participants were ineligible if they had 1) known lung anomalies or genetic conditions which may affect pulmonary function or MRI findings 2) contraindications for MRI, 3) any severe neurosensory impairment which might prevent test completion, or 4) a recent bacterial/viral respiratory illness (within the preceding 6 weeks)[13].

Study measures and procedures

Children wore a pedometer for one week, then came into the hospital for a study visit to complete a questionnaire, pulmonary MRI, and pulmonary function testing (PFT) on a single day.

Pedometer: Participants were sent a StepsCount Piezo Rx pedometer in the mail to wear at their waist for 7 consecutive days, including 2 weekend days. The pedometer collected daily step count (steps per day) as well as moderate-to-vigorous physical activity (MVPA) data, which is the duration of time (in hours) spent in moderate (100 steps per minute) or vigorous (120 steps per minute) activity[14]. This pedometer has been validated[14], and pedometer data has been shown to be a valid assessment of physical activity in school-aged children[15-18]. The pedometer was returned to the study team on the day of their study visit. Data was considered valid if a participant had at least 4 valid days (including one weekend day) of data.

Physical Activity Questionnaire (PAQ): The PAQ is a validated, self-report, recall questionnaire which documents the physical activity performed by a child in the most recent 7 days[19]. The outcome of interest was the PAQ global score, which is a composite score averaging the participation in several different activities to provide an indication of the degree of physical activity performed. A score of 1 indicates low physical activity, while a score of 5 indicates high physical activity[19].

Pulmonary MRI: Participants underwent a lung MRI to assess for average total proton density (at a lung volume of functional residual capacity plus one litre), which is a marker of lung tissue inhomogeneity, and average proton density at full expiration, which is an exploratory surrogate measure of gas trapping[13,20]. Novel research has identified correlations between pulmonary function and proton density,[21-23] but MRI measures provide different information about lung architecture[13].

Pulmonary function test: PFT included spirometry, which was conducted according to American Thoracic Society protocols[24]. Measurements included percent-predicted forced expiratory volume in one second (FEV1), forced vital capacity (FVC), forced expiratory flow at 25 and 75% of the pulmonary volume (FEF_{25-75}), residual volume (RV), and lung clearance index (LCI) using Global Lung Function Initiative (GLI) norms[25].

Medical chart review: Throughout the course of the study, a research coordinator collected medical history, including maternal and neonatal history, and medications.

Statistical analysis

The primary exercise measures were average daily steps, average daily MVPA measured by the pedometer, and the PAQ questionnaire score. Activity values that were extreme (2 standard deviations above or below average) were discarded to account for any technical errors or induced bias.

Associations between the average daily steps, average MVPA and PAQ score, with PFT and MRI measures, were conducted using Spearman correlations. We interpreted the absolute values of correlation coefficients as the following: 0.10-0.39 (weak), 0.40-0.69 (moderate), 0.70-0.89 (strong), and >0.9 (very strong) associations[26]. All statistical analyses were carried out using R version 4.0.3 (R Core Team, Vienna, Austria).

Separate multiple linear regression analyses were conducted to assess the association between each of our primary outcomes (average daily steps and average daily MVPA), respectively, with predictors of interest, including history of BPD (yes/no), FEV1% predicted and MRI total proton density. Sensitivity analyses examining the impact of recruitment site were conducted for each multiple linear regression. Unadjusted and adjusted estimates with 95% CI were reported.

To explore the impact of ADHD medication use on daily step count, we conducted an exploratory descriptive analysis comparing daily step count between children taking ADHD medication and those not taking ADHD medications, as well as a subgroup analysis only within the group with BPD.

RESULTS

There were 45 participants enrolled in this study, of which 28 met criteria for BPD in infancy, and 17 did not. Among several differences in the two groups of children, those with BPD had a lower gestational age at delivery, lower average birth weight, a greater percentage of males and lower height percentile at the time of evaluation (Table 1).

Of the 45 participants, 37 children had valid pedometer data and were included in the pedometer analyses. Five children were excluded due to insufficient days of recording, 2 children did not return their pedometer, and 1 had their data accidentally deleted prior to upload. An additional 4 participants of the 37 were missing data on MVPA due to pedometer data uploading issues at a single site.

Comparing children with and without history of BPD, there were no clear differences between the average number of daily steps, MVPA, or PAQ score (Table 2). Of the 37 participants with valid step count data, 27 had also had reliable PFT and MRI data. A Spearman correlation matrix was conducted to assess the correlation between daily step count, daily MVPA, PAQ score, PFT measures, and MRI measures (Table 3). While PAQ score was weakly correlated with both pedometer outcomes, there was a very strong correlation between average daily step count and average daily MVPA (r=0.90). A higher average daily step count was moderately correlated with higher FVC % predicted, lower LCI, and greater proton density at full expiration. A higher average daily MVPA was moderately correlated with higher FVC % predicted, higher TLC % predicted, lower LCI, and greater proton density at full expiration. All other pulmonary function measure associations were weak or negligible.

A linear regression analysis demonstrated an association between FEV1 % predicted and daily step count, after adjusting for MRI total proton density and BPD status. MRI total proton density and BPD status were not associated with average daily step count (Table 4a). A separate linear regression analysis with average daily MVPA as the outcome found similar results, with FEV1 % predicted marginally associated with average daily MVPA, after adjusting for MRI total proton density and BPD status (Table 4b). Sensitivity analyses examining the impact of site found that while it resulted in wider confidence intervals, the direction of association between FEV1 % predicted and both pedometer outcomes remained the same.

Of the 45 participants, 42 had medication data available. Of the 42 participants with available medication data, 6 were taking ADHD medications – 1 in the non-BPD group, and 5 in the BPD group. When we compared the average daily step count data by ADHD medication status, there were no differences between groups (Figure 1). Among children with BPD, the mean (standard deviation) daily step count of the 3/5 children who were taking ADHD medication for whom a valid step count was available, was 15772 (5054) compared to 16416 (4288) in the 21 children who were not taking ADHD medication (Figure 2).

DISCUSSION

With this study, we demonstrated a similar level of physical activity in children born extremely preterm, with and without BPD, both from objective pedometer data and self-reported activity level. Notably, after adjusting for both MRI total proton density and BPD status, a 5%-predicted increase in FEV1 was associated with approximately 750 more steps taken per day, suggesting that airflow limitation affects physical activity. Further, both higher daily step count and greater daily MVPA were moderately correlated with greater proton density at full expiration, suggesting less gas trapping.

Although we expected that there may be a difference between groups, levels of physical activity did not differ between children with and without BPD. Previous research has shown that children with BPD and lower FEV1 have reduced exercise capacity[5,10], and that children with BPD have pulmonary function abnormalities compared to their peers without BPD[7-9,11], which may correlate with physical activity limitations. Our study did find that lower physical activity levels were associated with pulmonary function abnormalities consistent with gas trapping, across both groups. This suggests that there may be factors related to extreme prematurity and lung function that affect physical activity, independent of the diagnosis of BPD, some of which may not be captured in this study, such as leg discomfort or being shorter than children without BPD, which may result in a greater number of steps needed to travel the same distance[27]. Diagnosing BPD relies on clinical characteristics and treatment, rather than physiologic or histologic changes, which may lead to misdiagnosis or misclassification of disease[28-30]. Tests which evaluate the lung function or structure, such as pulmonary MRI, may provide us with new information for diagnosis and classification of prematurity-associated lung disease, and may correlate better with functional measures such as physical activity[20,22,31-33].

Our study found that both lower daily step count and lower MVPA were correlated with diminished proton density at full expiration on MRI, a measure of gas trapping. In our previous PICTURE study, diminished MRI proton density at full expiration was correlated with PFT measures suggestive of gas trapping (higher RV/TLC and lower FEV1)[13], which have been shown to be associated with impaired exercise capacity in a previous study[34]. As pulmonary MRI measures may provide different and useful information compared to a clinical BPD diagnosis, further research is needed to understand factors that determine physical activity in this population[13].

Nonetheless, it was encouraging that the average number of steps taken by this cohort was significantly higher than expected when compared to CanPlay normative data for average step counts (11500-12200, depending on gender) in this age group[35]. Overall, our data suggest that children born extremely prematurely are more active than their peers, regardless of whether they were given a diagnosis of BPD in infancy. This is in contrast to a previous study suggesting that children born extremely preterm are less active than their term-born peers[5].

Given the high prevalence of ADHD and hyperactivity in children with history of extreme prematurity[36], we conducted analyses to determine if ADHD diagnosis explained differences in physical activity. While we

observed a lower step count in children with BPD who were treated with ADHD medications compared to their peers without ADHD medications, treated individuals still had a daily step count well above the average based on normative data. Ultimately, we found that there does not seem to be an effect of a diagnosis of or treatment for ADHD on overall activity level, although the prevalence of ADHD in the study population may be underreported or underdiagnosed[37]. This may account for the difference between our cohort and normative range data.

Our study was limited by small sample size. Although we increased the rigour of our study data by only considering children with valid pedometer data (i.e. at least 4 days of recording, including 1 weekend day), this further limited our sample. As such, our study was not powered to detect small differences between variables. Furthermore, our sub-analysis examining the impact of ADHD medications was unable to assess whether children with ADHD who are not treated with medication were present, limiting the reliability of this analysis. Children with untreated ADHD may be more active than their peers in all cohorts, which may account for the variation seen, however this is purely speculative. Lastly, due to the cross-sectional nature of this study, we could not evaluate the causal nature of the relationship between physical activity, BPD, PFT measures, and MRI indices.

Larger studies are needed to further evaluate the associations between pulmonary structure on MRI, pulmonary function and physical activity in children born extremely pre-term, with and without BPD. It would also be beneficial to reassess the physical activity level of this and similar cohorts of children as they approach adolescence and adulthood to determine if the participation and perception of physical activity level remains comparable to their peers, both between groups of BPD/non-BPD, and compared to non-preterm peers. These findings also support further research into novel imaging strategies which may provide alternate means to identify those at risk of impaired pulmonary function and lower physical activity, as the current clinical diagnostic classifications are limited in their ability to identify these children[31,32].

CONCLUSIONS

This study suggests that school-aged children born extremely prematurely have similar physical activity to their peers, regardless of a diagnosis of BPD in infancy. Nonetheless, pulmonary function measures suggestive of gas trapping and diminished proton density on MRI were associated with lower physical activity. These findings support ongoing encouragement of participation in physical activity programs in children born prematurely, particularly for children with more pulmonary abnormalities, who may become less physically active as they age.

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