Does moderate to vigorous physical activity improve lung function in children with cystic fibrosis in a real-world setting?

by

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Dalhousie University is located in Mi'kma'ki,
the ancestral and unceded territory of the Mi'kmaq.
We are all Treaty people.

Table of Contents

List of Tables

List of Figures

Abstract

Background: Cystic fibrosis (CF) is a rare genetic condition that causes multiorgan dysfunction, especially in the lungs (1). Airway clearance techniques are a fundamental component of CF care and are necessary to maintain lung function. In addition to airway clearance techniques (ACT), people with CF are encouraged to do daily moderate to vigorous physical activity to facilitate airway clearance and other general health benefits. Current evidence supporting the direct benefits of physical activity on lung function is inconsistent (2). A Cochrane Review and an updated literature review found three main gaps: the lack of objectively measured physical activity, observation periods shorter than six months, and inadequate sample sizes. This study aimed to address the gaps in the previous literature and to determine the association between objectively measured moderate to vigorous physical activity and FEV_1 among children with CF in the United Kingdom between 2018 and 2019.

Methods: Project Fizzyo was a longitudinal observational study of 145 children and young people with CF who were followed over 16 months in London, United Kingdom (3). Daily heart rate was measured as a proxy for moderate to vigorous physical activity using the Fitbit Alta HR. As there is no gold standard definition for moderate to vigorous physical activity using measures of heart rate for children, three available heart rate thresholds were used: 1) a fixed cut-off of 120 beats per minute (4), 2) a personalized age-specific heart rate reserve threshold (5) and 3) 70% of age-specific peak heart rate (6). Lung function measurements were modelled as a polynomial function to extrapolate sporadic measures to daily predicted FEV_1 (7). Linear mixed-effects models were used to estimate the association between moderate to vigorous physical activity and FEV_1. A separate model was developed for each heart rate threshold as the exposure. Biological sex, baseline age, baseline body mass index, baseline FEV_1, and quality of daily ACT were included as confounders.

Results: A total of 134 participants, with characteristics similar to those of the entire Project Fizzyo cohort, had complete clinical and Fitbit Alta HR data. Overall, the duration of moderate to vigorous physical activity was low for all participants, regardless of the threshold used. The total daily minutes of moderate to vigorous physical activity varied between the three thresholds: (Riddoch & Boreham median (IQR) 30 (9 – 64) minutes/day, Tanriver et al. 14 (4 - 31), and Swisher et al. 0 (0 – 3)). The effect sizes between continuous or categorical daily minutes of moderate to vigorous physical activity and FEV_1 were small and close to zero for all three thresholds. Similar results were observed for weekly minutes of vigorous physical activity. A sensitivity analysis was conducted for each threshold, only including days where participants had 500 minutes or more Fitbit Alta HR wear time. The results were similar to those of the main analysis.

Conclusion: Most participants did not meet the current WHO recommendations of an average of 60 minutes of moderate to vigorous physical activity daily, irrespective of which threshold was used. This may have led to a lack of evidence to interpret the main study objective. The lack of a gold standard heart rate threshold for moderate to vigorous physical activity for children makes it difficult to know which of the three thresholds is correct. Further, it may not be possible to interpret estimates of the association between physical activity and lung function if participants do very little activity overall. Further research is needed to objectively define and measure the intensities of physical activity for children.

List of Abbreviations Used

ACT	Airway clearance techniques
BPM	Beats per minute
CF	Cystic fibrosis
ECG	Electrocardiogram
FEV_1	Forced expiratory volume in one second
LMER	Linear mixed effects regression
WHO	World Health Organization

Chapter 1 Introduction

Cystic fibrosis (CF) is a rare genetic disease that devastates the lungs (1). Demanding treatments to maintain lung function often require more than 100 minutes each day and pose a significant burden on people with CF and their caregivers (8,9). People with CF are also encouraged to do daily physical activity because, in addition to other well-described health benefits, moderate to vigorous physical activity is thought to facilitate airway clearance and is hypothesized to improve lung function (10). Although physical activity is recommended for people with CF, the evidence supporting the direct benefit of physical activity on lung function in children with CF is inconsistent (2).

A recent Cochrane Review investigated the efficacy of physical activity interventions on lung function in people with CF and included 24 randomized controlled trials, of which 17 studies were also included in this literature review (2). The Cochrane Review showed low certainty evidence that physical activity interventions longer than six months improve lung function. The Cochrane Review highlighted a lack of studies with objective measures of physical activity, adequate sample sizes, and sufficient observation periods of habitual behaviours as the main research gaps (2). These three gaps were considered when developing the criteria to define high-quality studies for reviewing the literature in this research area.

The literature review conducted for this thesis identified 26 studies investigating the association between physical activity and lung function, including both high-quality (11,12) and low-quality (13–36) studies. High-quality studies included: 1. objective measures of physical activity or supervised physical activity, 2. an observation period longer than six months, and 3. an adequate sample size to detect a clinically meaningful effect size. Low-quality studies failed to meet one or more of the three high-quality study thresholds. Lung function was typically characterized by forced expiratory volume in one second (FEV_1) measured by spirometry. In previous literature, physical activity measures included pedometry (12), accelerometry (16,24,26,27), supervised exercise (11,14,15,18,22,23,25,28,32,36), and self-reporting (13,17,19–21,29–31,33–35). The study populations ranged from six to two hundred ninety-six subjects, and the observation periods ranged from an average of thirteen days to nine years. Across the 26 studies, the association between physical activity and FEV_1 was inconsistent, with 13 positive (11,25–36) and 13 non-significant (12–23,36) associations reported. However, none of the studies included in the literature review presented clinically meaningful associations between physical activity and lung function.

This thesis aimed to determine the association between objectively measured moderate to vigorous physical activity via heart rate and FEV_1 among children with CF in London, United Kingdom, between 2018 and 2019.

Chapter 2 Background

2.1 Cystic Fibrosis

Cystic fibrosis is caused by a genetic mutation in which the CF transmembrane conductance regulator protein is incorrectly produced or not produced at all (1). This genetic mutation results in multiorgan dysfunction, especially in the lungs (1). Currently, CF has no cure. Premature death occurs as a result of the recurrent cycle of infections and lung function decline (8). The incidence of CF varies between and within countries (37,38). In populations of white European descent, the incidence rate for CF is between 1 in 3000 and 1 in 6000 live births (37). It is estimated that approximately 100,000 individuals are living with CF globally (39). Even though CF is a rare disease, it causes an enormous burden to individuals, caregivers and society (9,40).

The burden of CF begins immediately following diagnosis and, in some cases, even before a diagnosis is made (41). The lungs are predominately affected by CF; the lack of effective chloride transport in the cell causes thick, sticky mucus to build up, predisposing the lungs to recurrent infections (1). Consequently, CF treatments mainly focus on maintaining lung function. A primary treatment for CF is ACTs to keep the lungs clear of mucus. Airway clearance includes both inhaled and mechanical therapies, which together can take over 100 minutes each day (42,43). Airway clearance techniques help loosen and remove mucus from the lungs, reducing infection risk and maintaining lung function (44). Different ACTs include chest physiotherapy, positive expiratory pressure therapy, high-pressure positive expiratory pressure therapy, and breathing techniques (44). The efficacy of airway clearance has historically been evaluated by comparing objective measures of lung function. Previous research has found that inhaled airway clearance (hypertonic saline and dornase alfa), as well as chest physiotherapy, are associated with improved FEV_1 in children with CF (1,45,46).

2.2 Lung Function

A spirometry test is the most common way to measure lung function. In this test, individuals take a full inhalation and forcefully breathe out as much as they can (47). The test specifically measures how much volume individuals can forcefully expire in the first second of the test. The primary outcome of this test is FEV_1, which is a measure of airflow (48,49).

People with CF typically receive medical care at a specialized CF centre at least quarterly. During a clinic visit, children older than six years with CF will have pulmonary function testing which FEV_1 measured using spirometry to assess disease progression. As CF lung disease progresses, FEV_1 values decline (50,51).

2.3 Physical Activity and Lung Function

In addition to the daily airway clearance therapies, all people with CF are encouraged to do daily physical activity. The association between physical activity and lung function in individuals with CF is less clear than the association between airway clearance and FEV_1 (2).

Physical activity encompasses a wide range of activities that can be incorporated into daily life, while exercise is a subgroup of physical activity made up of structured and organized activities (21,22). Low-intensity physical activity, such as walking at a comfortable pace, yoga, stretching, etc., do not increase stress on the cardiopulmonary system and are unlikely to activate specific processes that allow for airway clearance. Moderate to vigorous physical activity is a distinct type of physical activity and includes activities such as brisk walking, cycling, running and dynamic sports (54). These activities put stress on the cardiopulmonary system, which can increase ventilation, mechanical body vibration, and coughing, which can facilitate airway clearance and potentially improve lung function FEV_1 in people with CF (2).

Encouraging physical activity as a regular part of life for people with CF can allow them to feel more like everyone else whilst also improving their physical health (55). People with CF recognize the benefits of physical activity "...it would just help me feel more normal that I could manage something that I've got to manage as part of my CF by doing a regular activity that non-CF people do as well," an individual with CF stated during a community engagement focus group conducted in July 2021, as part of Project Fizzyo.

Although it is recommended that people with CF engage in physical activity, there is no gold standard definition of the heart rate threshold for moderate to vigorous physical activity for children, no clinical standard for the optimal intensity and duration of such activities, and it is unclear whether physical activity and exercise are beneficial for lung function.

2.4 Measuring Moderate to Vigorous Physical Activity

Several measures of moderate to vigorous physical activity are widely used in clinical and research settings, including self-report, supervision, pedometry, accelerometry, and heart rate monitors. Self-report measures of moderate to vigorous physical activity are inexpensive and straightforward to administer via interviews, daily diaries or questionnaires. Moderate to vigorous physical activity measures in self-reported questionnaires are limited by recall bias, different interpretations of guidelines, and overestimating activity, especially in children (56–59). Self-reported physical activity measures are challenging for children to recall certain intensities and duration of physical activity, mainly due to the sporadic nature of activity (56). Children between the ages of 11 and 13 can only recall 40 percent of the activities they completed in the past week and only up to 65 percent of the activities in the past day (60). To mitigate measurement error and increase accuracy, objective measures of physical activity or supervised physical activity can reduce or eliminate recall bias and measurement error of self-reported measures.

Supervised physical activity can eliminate the need for participants to recall the intensity and duration of activity. Supervised physical activity is completed in a facility under the observation of professionals (e.g., physiotherapists, fitness trainers) who can document physical activity completion in terms of duration, intensity, frequency and type (61). Professionals have a better understanding when it comes to estimating the duration or intensity of physical activity compared to participants, but still rely on subjective impressions of moderate to vigorous activity.

Objective measures of physical activity, such as pedometers, accelerometers, and heart rate monitors, have the potential to reduce bias and reporting errors. Pedometers measure physical activity by recording steps over time, which can measure speed and distance (56). Pedometers are an inexpensive option for measuring physical activity (56) but are insensitive to physical activity intensity, frequency, and duration (58). Accelerometers measure the frequency and magnitude of the body's acceleration during movement, which can be further translated into the metric of interest, such as intensity and duration (56,58). However, accelerometers require technical expertise, specialized software and hardware, and the devices are expensive (58). Heart rate monitors give an objective but indirect measure of physical activity frequency, intensity and duration (56). Wearable trackers that measure heart rate are mainly inexpensive and unobtrusive (56). The main limitation is that heart rate can be influenced by other factors, such as emotions, anxiety levels, baseline level of physical fitness, hydration, nutrition, and the environment (4), which can elevate heart rate and incorrectly classify low-intensity activity as moderate or potentially vigorous physical activity.

2.4.1 Defining Moderate to Vigorous Physical Activity

Although heart rate is not a direct measure of physical activity, it is commonly used as a proxy as it indicates the amount of stress on the cardiovascular system (62). Heart rate is a physiological indicator of physical activity as well as energy expenditure (58). Intensity, duration, frequency, and levels of physical activity can be measured using heart rate (58). There are two standards to define moderate to vigorous physical activity in terms of heart rate for healthy adults (63,64). MacIntosh et al. define moderate physical activity as 64 to 76 percent of maximum heart rate and vigorous physical activity as 77 to 93 percent of maximum heart rate in healthy adults (63). The American College of Sports Medicine defines moderate physical activity as 64 to 76 percent of maximum heart rate and vigorous physical activity as 77 to 95 percent of maximum heart rate in healthy adults (64). Maximum heart rate can vary between individuals due to many factors such as age, fitness level, and health status (65–67), and existing definitions may not be appropriate for children.

Riddoch & Boreham suggested a peak heart rate above 120 bpm (4) as a definition of moderate to vigorous physical activity in children. This recommendation may not be applicable to children of all ages and health statuses, as peak heart rate declines with age (37), and people with CF tend to have higher heart rates than healthy individuals (67). Whether this approach by Riddoch & Boreham is appropriate for children with chronic conditions like CF is unclear.

Another approach developed by Tanriver et al. to further personalize the definition of moderate to vigorous physical activity was adapted from the American College of Sports Medicine's heart rate reserve method (68). This method was developed to incorporate within and between-person variability of heart rate and provide an objective way of determining minutes of moderate to vigorous physical activity for children. The methods proposed by Tanriver et al. may not always be feasible to calculate as peak and resting heart rate measurements are not always available, so a simplified approach may be more appropriate.

To simplify the personalized threshold proposed by Tanriver et al., a percentage of peak heart rate can be used to define moderate to vigorous physical activity (6). Swisher et al. defined moderate to vigorous physical activity as 70 percent of maximal or peak heart rate in children ages seven to nineteen with CF (6). As peak heart rate measures are challenging to obtain in clinical and real-world settings, the age-specific peak heart rate equation from Tanriver et al. can be simplified and implemented in practice. Some similar measures of heart rate and different measures of physical activity were utilized in other studies, such as those included in the most recent Cochrane Review.

2.5 Cochrane Review

The most recent Cochrane Review by Radke et al., 2022, aimed to assess how physical activity interventions impacted exercise capacity outcomes, including peak oxygen uptake, lung function, and health-related quality of life (2). The review included 24 parallel randomized controlled trials with 875 participants in total, of which 17 of the studies were included in the literature review conducted for this thesis. The main findings of the Cochrane Review were that interventions lasting longer than six months would likely improve exercise capacity outcomes compared to no physical activity or exercise. Individuals in the physical activity intervention groups had a mean change in FEV_1 percent predicted of 2.41 percent (0.49 percent lower to 5.31 percent higher (95% CI)) compared to the control group, which does not meet the three percent minimal clinically important difference (69).

In a sub-analysis, Radke et al. found that from 367 participants in six randomized controlled trials, there was low-certainty evidence that physical activity intervention had little to no effect on FEV_1 compared to control groups (2). In a sensitivity analysis of five studies lasting one to two years, intervention groups performing physical activity had higher FEV_1 values compared to control groups. Four observational studies, longer than one year, were discussed in the review and also showed that physically active individuals had slower FEV_1 decline than inactive individuals. The Cochrane Review concluded that FEV_1 differences need to be observed over a period longer than six months while completing a physical activity programme.

2.6 Research Gaps

Based on the Cochrane Review, there was a lack of high-quality studies investigating the association between habitual moderate to vigorous physical activity and FEV_1. Three main research gaps were evident: studies that included objective measures of physical activity, an observation period longer than six months, and a statistically sufficient sample size. These research gaps were also used to guide the literature review included in this study (2).

2.7 Previous Literature on the Association between Physical Activity and FEV_1

A search of PubMed using the terms, (Physical Activity OR Exercise) & (Cystic Fibrosis OR CF) & (Child OR Children OR Adolescents), resulted in 1367 records, of which 26 included physical activity as an exposure and FEV_1 as an outcome for people with CF. The literature review only included published articles and did not select any abstracts. All articles included in the literature review are summarized in Table 1.

The studies identified in the literature review were classified as high-quality studies if they included objective measures or supervised physical activity, an observation period longer than six months, and an adequate sample size to detect a clinically meaningful effect size.

Adequate sample size was defined as having enough power to detect a clinically meaningful difference in lung function of at least three percent over six weeks (69). To detect a three percent difference in lung function, with an eight percent standard deviation, a five percent significance level and eighty percent power, a sample size of 112 participants in the intervention group and 112 in the control group is needed. However, comparing this clinically meaningful difference in lung function to studies with varying durations is challenging. Studies were classified as low-quality if they lacked one or more high-quality study criteria. These criteria were developed with consideration to the Newcastle-Ottawa Quality Assessment Scale and the research gaps from the Cochrane Review, incorporating the criteria that can impact physical activity and lung function studies in individuals with CF (70).

Table 1 Summary of previous studies investigating the association between physical activity and forced expiratory volume in one second in cystic fibrosis.

Study Quality	Study	Association	Physical Activity Measure	Physical Activity Dose	Sample Size	Study Duration
High-Quality	Elce et al., 2018	Positive	Supervised	Physical exercise sessions	118	3 years
	Hebestreit et al., 2022	No association	Pedometer & Self-report	3 hours of vigorous activity added per week	117	1 year
Low-Quality	Beaudoin et al., 2017	No association	Self-report	3 training sessions per week (20-40 minutes)	14	13 weeks
	Carr et al., 2018	No association	Supervised	8 sessions over 3 months	40	9 months
	Donadio et al., 2022	No association	Supervised	60 minutes 3 times per week	25	8 weeks
	Gruber et al., 2022	No association	Accelerometer	30 minutes 5 times per week	6	1 year
	Gupta et al., 2019	No association	Self-report	All daily activity	52	1 year
	Hebestreit et al., 2010	No association	Partially supervised	Add 60 minutes sport activity 3 times per week	38	2 years
	Hommerding et al., 2015	No association	Self-report	20 minutes at least 2 times per week	34	3 months
	Klijn et al., 2004	No association	Self-report	All daily activity	20	3 months
	Rovedder et al., 2014	No association	Self-report	Daily strength training	41	3 months
	Santana-Sosa et al., 2012	No association	Supervised & Heart rate monitor	30-50 minutes 3 times per week	22	3 months
	Santana-Sosa et al., 2014	No association	Supervised & Heart rate monitor	30-60 minutes of 3 times per week	20	3 months
	Selvadurai et al., 2004	No association	Accelerometer & Self-report	All daily activity	296	14 days

Study Quality	Study	Association	Physical Activity Measure	Physical Activity Dose	Sample Size	Study Duration
Low-Quality	Cerny et al., 1989	Positive	Supervised	15-20 minutes per day	17	13 days
	Cox et al., 2016	Positive	Accelerometer	All daily moderate to vigorous physical activity	65	1 year
	Cox et al., 2018	Positive	Accelerometer	All daily moderate to vigorous physical activity	65	3 years
	Güngör et al., 2021	Positive	Supervised	Daily postural exercises	22	6 weeks
	Kriemler et al., 2013	Positive	Self-report	30-45 minutes 3 times per week	39	2 years
	Moorcroft et al., 2004	Positive	Self-report	20 minutes 6 times per week	51	1 year
	Paranjape et al., 2012	Positive	Self-report	20-30 minutes of moderate to vigorous physical activity 5 times per week	65	2 months
	Sawyer et al., 2020	Positive	Supervised	10-minute sessions	14	8 weeks
	Schneiderman-Walker et al., 2000	Positive	Self-report	All daily activity	65	3 years
	Schneiderman-Walker et al., 2005	Positive	Self-report	All daily activity	109	2 years
	Schneiderman et al., 2014	Positive	Self-report	All daily activity	212	9 years
	Selvadurai et al., 2002	Positive	Supervised	5 sessions per week	66	18 days

2.7.1 High-Quality Studies

Two of the 26 studies were considered high-quality. Even though these two studies were statistically underpowered, they will be considered high-quality as they used objective or supervised physical activity and had observation periods longer than six months.

One of the two high-quality studies included Elce et al., 2018, which demonstrated a slower decline in FEV_1 over three years in individuals in the physical activity group compared to the sedentary group (11). This observational study observed 59 adults in the intervention group and 59 healthy controls utilizing supervised physical activity training classes over three years. This study may have been underpowered to find a clinically meaningful difference in lung function, as there were fewer than 112 participants in each group. The physical activity classes were performed outside the CF centres, and the instructors reported the weekly physical activity to the research team. Individuals may have participated in physical activity outside of the weekly supervised classes, which would not have been included in the physical activity reported by the instructors. Therefore, this could misclassify participants' duration and intensity of physical activity. Also, this study found a 1.2 percent between-group difference in FEV_1 over three years, which is not clinically meaningful.

The other high-quality study by Hebestreit et al. 2022, was the first large, randomized controlled trial that attempted to investigate the impact of a physical activity intervention on lung function in children with CF (12). This trial involved 117 participants, which fell short of the 292 participants the researchers aimed for in their power calculation. This indicates that the study may have been underpowered, as there were only 60 participants in the intervention group and 57 in the control group, not meeting the required sample size of 224 participants in total to detect a clinically meaningful change in lung function. The intervention group was asked to add three hours of vigorous physical activity to their current weekly routine, while the control group was asked to keep their physical activity levels constant. Physical activity was measured using self-report diaries and pedometry over the 12-month period. Vigorous physical activity was documented daily by type of exercise and duration in self-report diaries (71). Daily step count, aerobic step count (more than ten consecutive minutes with 60 steps per minute) and time in sedentary activities were also documented (71). This study showed that vigorous physical activity resulted in unchanged FEV_1 in the intervention group, while FEV_1 values improved in the control group. Hebestreit et al. explained that the results were unclear and unexpected, but 25% of the participants in the control group reported an increase in vigorous physical activity of 30 minutes per week over the first six months (12). The adherence in the intervention group was only 56% over the entire study period, which could have impacted the results as well.

Overall, given that the two high-quality studies were statistically underpowered, it emphasizes the need for future high-quality studies that are adequately powered with objective measures and sufficient duration to find a clinically meaningful difference in FEV_1.

2.7.2 Low-Quality Studies

Of the 26 studies identified in the literature review, 24 were considered low-quality. These low-quality studies had observation periods ranging from an average follow-up period of 13 days to nine years and had a range of six to 296 participants (Table 1). The measures of physical activity included self-reporting, accelerometers, and supervision (Table 1). The low-quality studies reported positive and no significant associations between physical activity and FEV_1; 12 of the 24 studies showed a positive association (25–36), whereas 12 showed no significant associations (13–24). None of the low-quality studies reported a negative association, which could indicate a publication bias. Fifty percent of the low-quality studies with positive associations used self-reported measures (29–31,33–35); it is possible that self-reported physical activity was overreported. The inconsistent results, measures of physical activity, inadequate sample sizes and observation periods demonstrate the need for future high-quality studies to determine the association between physical activity and FEV_1.

Chapter 3 Objective

To determine the association between objectively measured moderate to vigorous physical activity via heart rate and FEV_1 among children with cystic fibrosis in London, United Kingdom, between 2018 and 2019.

Chapter 4 Methods

4.1 Study Design

The target population for the study was children with CF. Data from Project Fizzyo was used for this study. Project Fizzyo was a longitudinal observational study based in London, United Kingdom and included 145 participants between the ages of six and sixteen years (3). Participants with a clinical diagnosis of CF followed at one of the paediatric centers participating in the project (Great Ormond Street Hospital, Royal London Hospital, the Royal Brompton Hospital, or a shared patient between these centres) were eligible to participate. Recruitment for Project Fizzyo began at the three participating hospitals on September 10, 2018, and lasted until July 1, 2019. Participants were enrolled in Project Fizzyo for a period of 16 months following their recruitment date. Participants were excluded if they had previously undergone a lung transplant or had another clinically significant medical condition other than CF. The participants were instructed to continue their standard medications, physiotherapy, and physical activity prescriptions.

4.2 Outcome

The main outcome of this study was FEV_1. FEV_1 was assessed at multiple time points throughout Project Fizzyo before or at least one hour after resting from exercise assessments (3). Additional FEV_1 measures from clinic visits were also included in Project Fizzyo data. Measured FEV_1 values were converted to percent predicted relative to the height, age and sex of a healthy population using Global Lung Function Initiative equations (72).

To align daily or weekly physical activity data (exposure) with FEV_1 (outcome), a polynomial equation was developed to extrapolate the predicted FEV_1 for each individual at a given time point (7). Figure 1 is a visual representation of how the polynomial function (yellow) predicted measures of FEV_1 to match with the daily measures of heart rate data (black) for one individual over a five-year period.

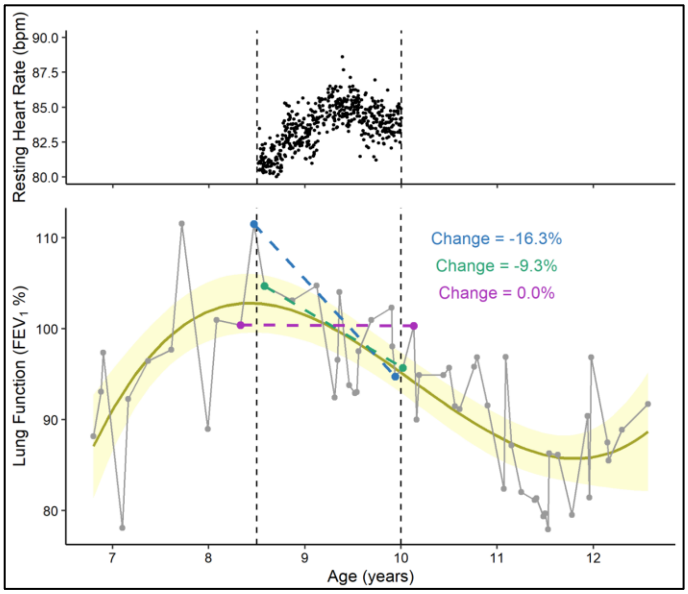


Figure 1 Comparison of asynchronous FEV_1 measures (grey) to daily heart rate measures (black), with flexible FEV_1 polynomial (yellow). *Adapted from Filipow et al., 2023, with no changes made to the figure (7). Link to the Creative Commons license: https://creativecommons.org/licenses/by/4.0/

The grey points represent the observed lung function measures taken over the five-year period, which are sporadic. If different observed measures are used to determine the change in lung function throughout Project Fizzyo (vertical dashed lines), the results vary depending on which points are chosen.

4.3 Exposure

The main exposure variable in this study was moderate to vigorous physical activity. Each Project Fizzyo participant was given a Fitbit Alta HR. Participants were asked to wear the Fitbit activity trackers during all waking hours except when bathing or swimming, as they were not waterproof. The trackers were also not worn when being synced or when charging.

The Fitbit Alta HR had a photoplethysmographic sensor to measure heart rate (3). The sensors collected heart rate data approximately 6 to 30 times every minute, depending on activity level. Higher heart rates triggered the Fitbit Alta HR to increase sensor frequency. Since the sensor collection varied per minute, the heart rate data were averaged per minute. The daily average resting heart rate was then calculated for each participant. Near maximal exercise capacity (25-level 10-meter incremental shuttle walk test, with both Polar H10 heart rate monitor and Fitbit Alta HR) was assessed routinely throughout Project Fizzyo. Peak heart rate values were taken following the exercise capacity assessments. With both resting and peak heart rate values for all participants it was possible to use a threshold to calculate when individuals were in moderate to vigorous physical activity. Missing values were not imputed as they were not missing completely at random. Some participants could not wear their Fitbit at school, and wear time was not completely random. Participants may have also only chosen to wear their Fitbit when they were doing physical activity.

Subsequently, the cumulative number of minutes each day above each of the three thresholds (Table 2) for moderate to vigorous physical activity was calculated as the main exposure variable. To calculate moderate to vigorous physical activity threshold, raw heart rate data were cleaned using the R pipeline. The R pipeline was developed to summarize clinical data collected as part of Project Fizzyo, with the pipeline described in the Project Fizzyo Protocol (3). Then, each minute of heart rate data was examined to determine if it was above the moderate to vigorous physical activity threshold. To determine the daily and weekly minutes of moderate to vigorous physical activity, all minutes when the heart rate was above the threshold were added together for each participant daily and weekly.

The three moderate to vigorous physical activity thresholds each have strengths and limitations. The fixed threshold by Riddoch & Boreham did not consider age, unlike the other two thresholds that considered age when calculating the moderate to vigorous physical activity threshold. As peak heart rate declines with age in childhood, this could have impacted physical activity estimates between thresholds (66). While there is no gold standard physical activity threshold in terms of heart rate, it was challenging to compare the three thresholds.

Table 2 Three thresholds for defining moderate to vigorous physical activity. Each criterion uses heart rate as a proxy for moderate to vigorous physical activity, using peak and resting heart rates in equations to classify heart rate per minute. Participant ID is represented by i, and j represents a given time point.

Generalized Recommendation Riddoch & Boreham, 1995	**Minutes when peak heart rate is above 120bpm** Peak heart rate (PHR) $PHR_j > 120$ bpm
Personalized Moderate to Vigorous Physical Activity (MVPA) Equation Tanriver et al., 2024	**Minutes of MVPA are defined by the following:** Resting heart rate (RHR) $RHR_{ij} = 85.41 - 0.99\ age_{ij}$ $PHR_j = 201.89 - 0.51\ age_j$ $\text{MVPA Threshold}_{ij} = RHR_{ij} + 0.4 * (PHR_j - RHR_{ij})$
Percentage of Peak Heart Rate Swisher et al., 2015	**Minutes above 70 percent of peak heart rate** $0.70 * PHR_j = 0.7 * (201.89 - 0.51\ age_j)$

Table 3 Continuous and categorical moderate to vigorous physical activity variable definitions based on Table 2.

Continuous		**Categorical**	
Daily	**Weekly**	**Daily**	**Weekly**
Sum of minutes of moderate to vigorous physical activity for each day.	Sum of minutes of moderate to vigorous physical activity for each 7 day week.	0 – 30 minutes 30– 60 minutes 60 + minutes	0 – 60 minutes 60 – 120 minutes 120 + minutes

4.4 Confounders

Biological sex, baseline age, baseline body mass index, ACT quality and baseline FEV_1 were considered potential confounding variables (Figure 2). The baseline was the first measurement collected in Project Fizzyo. Biological sex was included as anatomical and functional differences exist between the shape and function of the male and female lung (73), and CF lung disease progresses differently between males and females (74). There are also differences between male and female participation in moderate to vigorous physical activity (34). Baseline age was included because age can affect the duration and intensity of physical activity (75,76), and FEV_1 measures progressively worsen with age in people with CF (50,51). Baseline body mass index was included as there is an association between body mass index and daily physical activity (77), and there is an association between body mass index and FEV_1 (78). Baseline FEV_1 was included because healthier participants may be more likely to do physical activity (Figure 2). Airway clearance technique quality was included in the analysis as there is an association between ACT quality and FEV_1 (46) , and individuals who have better ACT quality may more regularly perform moderate to vigorous physical activity.

4.5 Analysis

4.5.1 Data Preparation

All variables were examined to check for biologically implausible observations and, therefore, were outliers. To determine if an observation was biologically implausible, they were compared to other values for that participant and the literature for people with CF of similar age and disease severity. Correlation between covariates was assessed to check for multicollinearity between variables. To assess multicollinearity for continuous variables, if the variance inflation factor was higher than ten, one of the variables was removed from the analysis (79). Scatterplots were used to check whether the relationships between continuous variables were linear.

4.5.2 Data Exploration

Descriptive statistics for each variable for the study population were summarized in Table 5. The mean and standard deviation were presented for continuous variables, such as age, baseline body mass index, etc. For non-normally distributed variables, the median and interquartile range were presented. Categorical variables, such as biological sex, participants per hospital center, etc., were summarized as counts and percentages in each category. The entire Project Fizzyo cohort was summarized in Raywood et al., 2023 (80) and compared to the participants included in this study.

4.5.3 Model Building

To begin, a crude model of the association between moderate to vigorous physical activity threshold and FEV_1 was created using a linear mixed-effects regression model; none of the covariables were included. The autoregressive correlation structure was used in the analysis to account for the correlated nature of repeated measurements in the same individual. Each of the three moderate to vigorous physical activity thresholds were the main exposure variable in separate models. An adjusted model, including biological sex, baseline age, baseline FEV_1, baseline body mass index, and ACT quality, was used to estimate the effect adjusted for confounding variables. To check for confounding, the FEV_1 slopes were compared in the crude and adjusted models; a 10% change in the slope was used to suggest confounding.

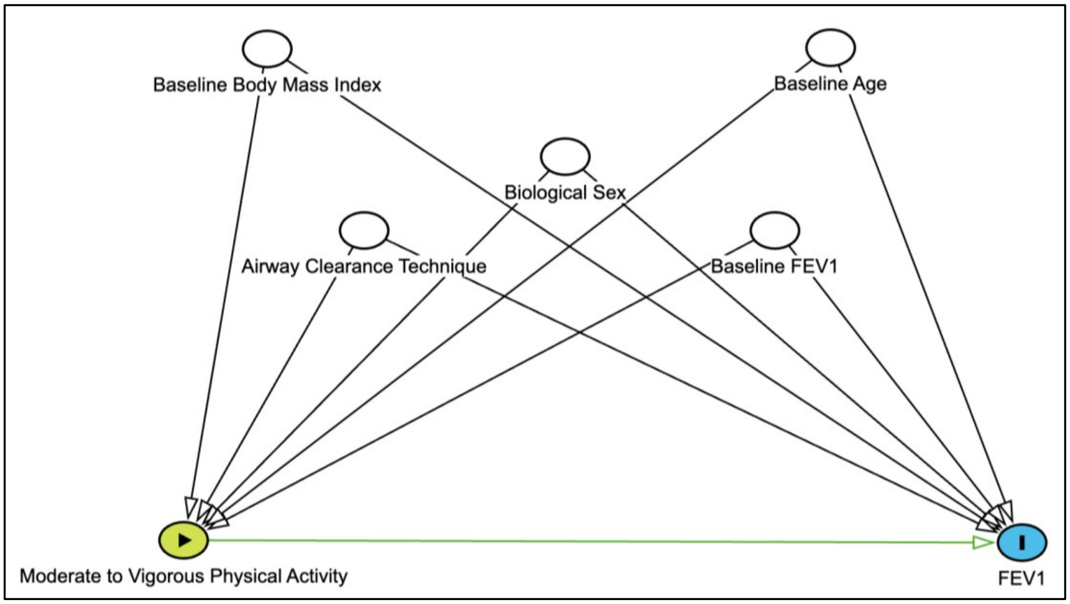


Figure 2 Directed acyclic graph showing how all confounders are associated with exposure (moderate to vigorous physical activity) and outcome (FEV$_1$*).*

The regression assumptions were examined to check whether the residuals showed homoscedasticity; the residuals were plotted against time to check for a random scatter of data points. A quantile-quantile plot assessed whether the residuals were normally distributed. dfBeta analysis identified potential influential outliers and flagged data points were further investigated. The cut-off point for influential outliers in dfBeta analysis was $\frac{2}{\sqrt{n}}$ and anything above that value was flagged.

4.6 Sensitivity Analysis

A sensitivity analysis was performed on individuals who wore the Fitbit Alta HR device for more than 500 minutes daily for the 16-month Project Fizzyo study period.

4.7 Power Calculation

Filipow et al. analyzed the effectiveness of ACTs on lung function using the Project Fizzyo data and found that each additional good quality ACT completed during the week was associated with an increase in FEV$_1$ % predicted of 0.056 (46). Since ACTs have traditionally been the primary method of improving mucus clearance in people with CF, the maximum effect size for this study is not likely to exceed 0.056.

With 145 participants and an average of 59 weeks of data per participant, a sample size of 2474 observations would have 80% power to detect a difference of 0.05 with an alpha level of 0.05 (Table 4). Since it is expected that the association with physical activity will not be as strong, a sample size of 8555 observations would have sufficient power to detect an effect size of 0.027 (Table 4).

The necessary input variables were unavailable to effectively estimate the longitudinal sample size for linear mixed effects regression. Therefore, another method was used, which could impact the sample size and power calculation.

Table 4 Sample sizes needed to detect certain effect sizes, with a power of 80% and an alpha level of 0.05.

Effect Size	**Observations**
0.027	8555
0.03	6871
0.04	3865
0.05	2474

Chapter 5 Results

5.1 Study Population

Project Fizzyo included 145 participants between the ages of six and seventeen; 142 submitted Fitbit data, and 134 also had complete clinical data with FEV_1 measures. Further demographic characteristics of the study population (n=134) are summarized in Table 5. The mean (standard deviation) age of the study population was 10.2 (2.9) years, and the majority (85.8 percent) of the participants were of white European ancestry (Table 5). The entire Project Fizzyo cohort was summarized in Raywood et al., 2023 (80) and the subgroup (n=134) included in this study were similar in terms of demographic characteristics (Table 5).

5.2 Descriptive Statistics

Table 5 summarizes the daily moderate to vigorous physical activity calculated using the three thresholds. It also summarizes the proportion of days above the World Health Recommendation (WHO) of 60 minutes of moderate to vigorous physical activity for each threshold.

Table 5 Demographic characteristics of study participants who met the inclusion threshold for Project Fizzyo and had Fitbit Alta HR and clinical data for the current study.

		Units	Current Study	Raywood et al., 2023
Participants		n	134	145
Males		n (%)	64 (47.8)	74 (51.0)
Females		n (%)	70 (52.2)	71 (49.0)
Participants Per Hospital	**Great Ormond Street Hospital**	n (%)	72 (53.7)	75 (51.0)
	Royal Brompton Hospital	n (%)	33 (24.7)	40 (28.0)
	Royal London Hospital	n (%)	29 (21.6)	30 (21.0)

		Units	Current Study	Raywood et al., 2023
Age (years)		mean (SD)	10.2 (2.9)	10.2 (2.9)
Ethnicity	**White**	n (%)	115 (85.8)	124 (85.5)
	Black	n (%)	2 (1.5)	3 (2.1)
	East Asian	n (%)	0 (0.0)	0 (0.0)
	Other	n (%)	17 (12.7)	18 (12.4)
Baseline Lung Function (% predicted FEV_1)		mean (SD)	87.8 (15.5)	88.3 (15.4)
Baseline Body Mass Index Z-Score		mean (SD)	-0.02 (0.9)	0.08 (0.9)
Resting Heart Rate (BPM)		mean (SD)	75.8 (9.3)	Not Reported
Peak Heart Rate (BPM)		mean (SD)	193.7 (14.0)	
Steps per Day		mean (SD)	8854 (5079)	
Fitbit Wear Time per Day (minutes)		median (IQR)	879.0 (658.0 – 1334.0)	
Days in Project Fizzyo		mean (SD)	363.7 (175.0)	
Days with Fitbit Data		median (IQR)	175.0 (67.8 – 330.3)	
Daily minutes of moderate to vigorous physical activity				
Riddoch & Boreham, 1995 Threshold		median (IQR)	30.0 (9.0 - 64.0)	
Tanriver et al., 2024 Threshold		median (IQR)	14.0 (4.0 – 31.0)	
Swisher et al., 2015 Threshold		median (IQR)	0.0 (0.0 - 3.0)	
Proportion of days above 60 minutes of moderate to vigorous physical activity				
Riddoch & Boreham, 1995 Threshold		median (IQR)	20.0 (5.0 – 37.0)	
Tanriver et al., 2024 Threshold		median (IQR)	5.0 (1.0 – 13.0)	
Swisher et al., 2015 Threshold		median (IQR)	0.0 (0.0 – 0.2)	

Overall, all participants had very low minutes of moderate to vigorous physical activity throughout the 16-month study period. The median (IQR) days with zero minutes of moderate to vigorous physical activity per participant were 85 (26.3 – 146.0) using the Swisher et al. threshold, whereas the median (IQR) days with zero minutes of moderate to vigorous physical activity per participant were 17.9 (4.3 – 20.0) and 19.5 (8.0 – 30.0) using the Riddoch & Boreham and Tanriver et al. threshold, respectively. The percentage of days with zero minutes of moderate to vigorous physical activity for each threshold is presented in Figure 3. Riddoch & Boreham produced 2396 days with zero minutes of moderate to vigorous physical activity, Tanriver et al. produced 2963 days, and Swisher et al. produced 14201 days out of the 25507 days with Fitbit data for all participants.

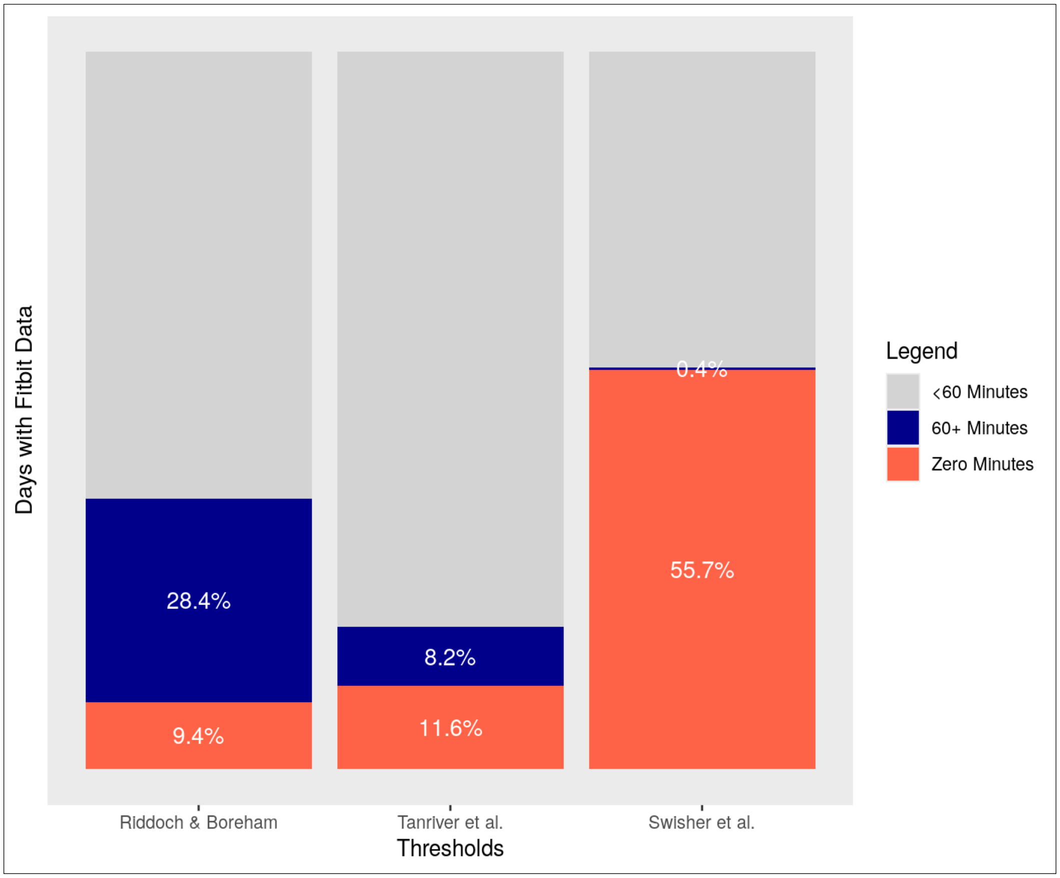


Figure 3 Bar plot comparing the days with zero minutes and 60 minutes of moderate to vigorous physical activity for each threshold out of all days with recorded Fitbit data for all participants combined (n=25507 days).

The days with zero minutes of moderate to vigorous physical activity for each threshold were removed to create a violin plot to show the distribution of daily physical activity minutes (Figure 4). In Figure 4, the Riddoch & Boreham threshold included 134 participants, Tanriver et al. included 133 participants, and Swisher et al. included 132 participants. These distributions are skewed, as there are more days with low minutes of moderate to vigorous physical activity for all three thresholds (Figure 4).

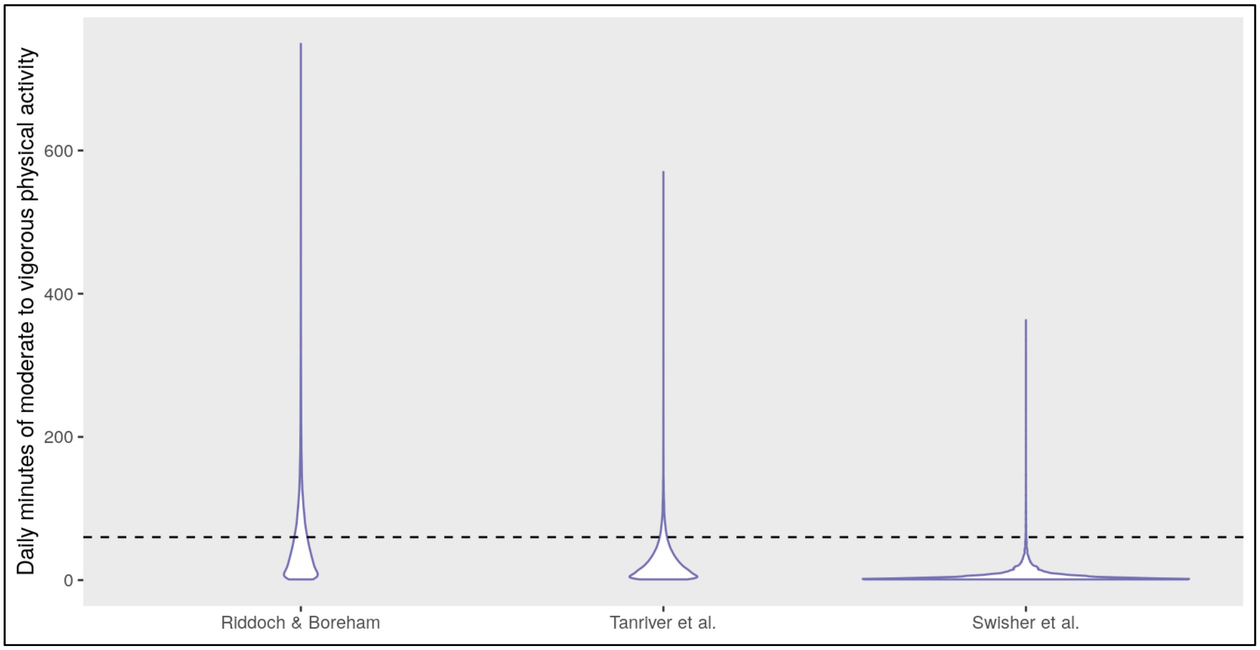


Figure 4 Violin plot of daily minutes of moderate to vigorous physical activity for the three thresholds compared to the WHO recommendation (dashed black line at 60 minutes), with all days with zero minutes removed (Riddoch & Boreham 2396 removed, Tanriver et al. 2963 removed and Swisher et al. 14201 removed).

Stacked bar graphs were created for each threshold to further understand the proportion of days that met the WHO moderate to vigorous physical activity recommendation of an average of 60 minutes daily (Figure 5, Figure 6, Figure 7). Figure 5, Figure 6, and Figure 7 all show very limited proportions of days with 60 minutes of moderate to vigorous physical activity for all participants. The median proportion of days with 60 minutes or more of moderate to vigorous physical activity using the Riddoch & Boreham threshold was 20 percent for all study days for all participants (Table 5). The Tanriver et al. threshold showed a median of 5 percent of days, and Swisher et al. showed a median of 0 percent of days (Table 5).

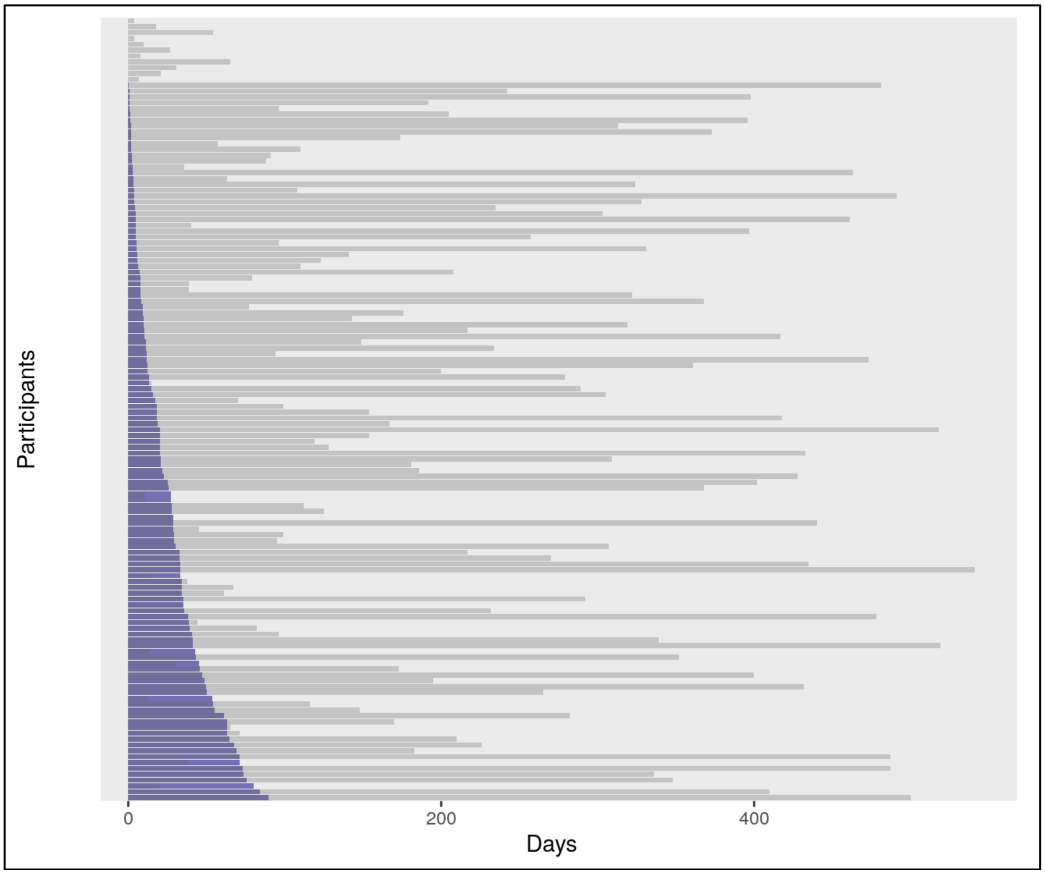


Figure 5 Proportion of days with 60 minutes of moderate to vigorous physical activity (purple) out of all days with Fitbit Alta HR data (dark grey) for each participant ID (n=134) using the Riddoch & Boreham moderate to vigorous physical activity threshold.

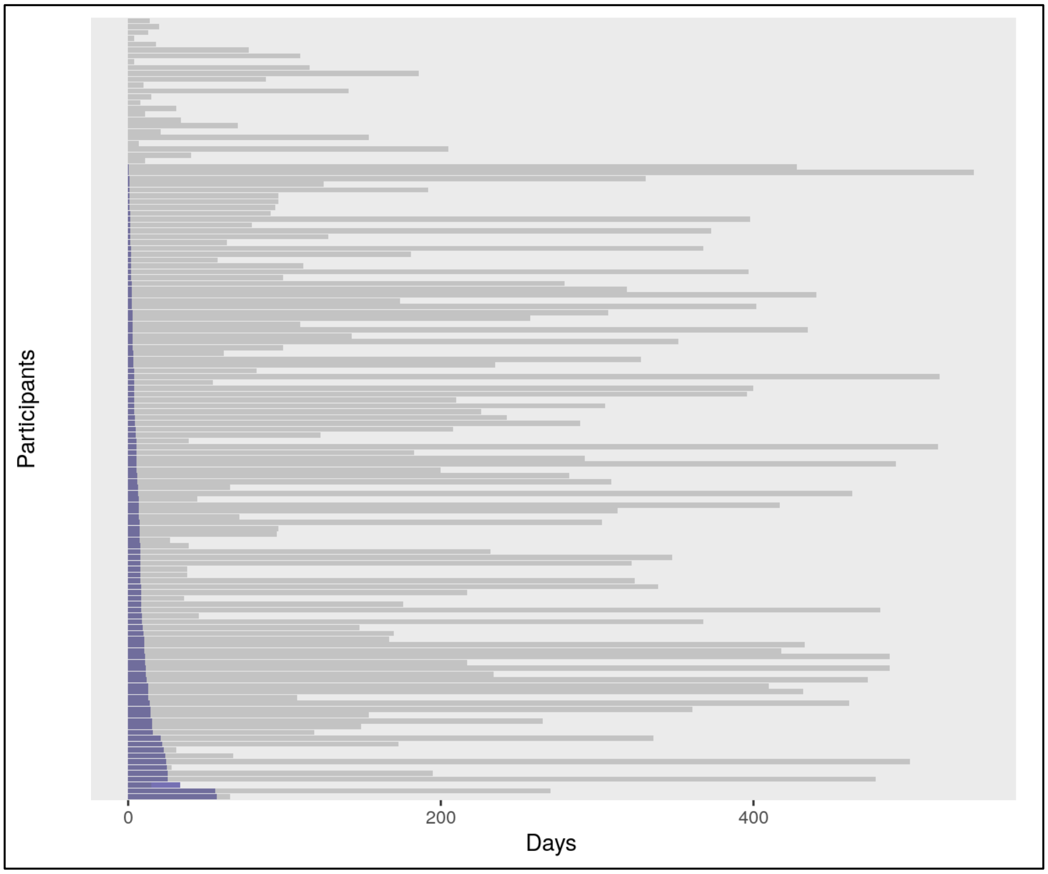


Figure 6 Proportion of days with 60 minutes of moderate to vigorous physical activity (purple) out of all days with Fitbit Alta HR data (dark grey) for each participant ID (n=134) using the Tanriver et al. moderate to vigorous physical activity threshold.

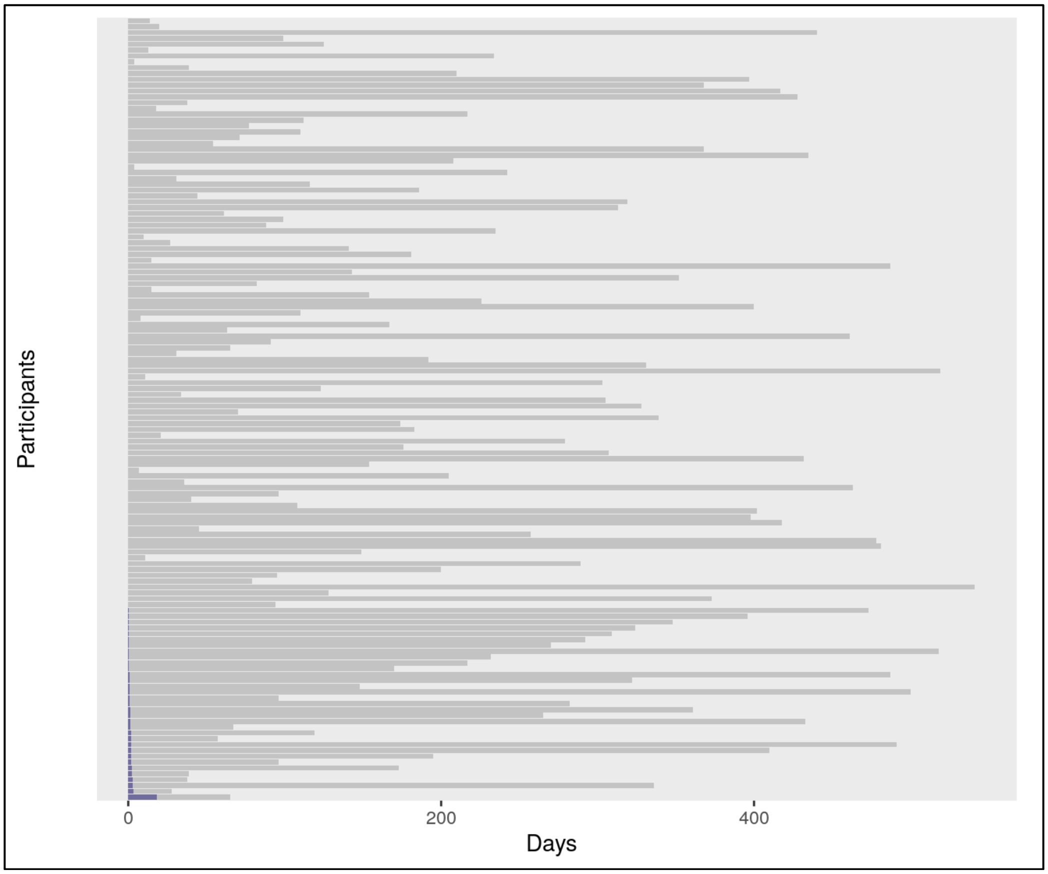


Figure 7 Proportion of days with 60 minutes of moderate to vigorous physical activity (purple) out of all days with Fitbit Alta HR data (dark grey) for each participant ID (n=134) using the Swisher et al. moderate to vigorous physical activity threshold.

Minutes of moderate to vigorous physical activity among the participants were visualized as a function of baseline age (Figure 8). This figure showed an age dependency for the Riddoch & Boreham threshold, as younger participants had higher average minutes of moderate to vigorous physical activity. The minutes of moderate to vigorous physical activity decreased as baseline age increased. The Tanriver et al. and Swisher et al. physical activity thresholds did not show a dependency on baseline age because these two thresholds account for age in the calculation for moderate to vigorous physical activity.

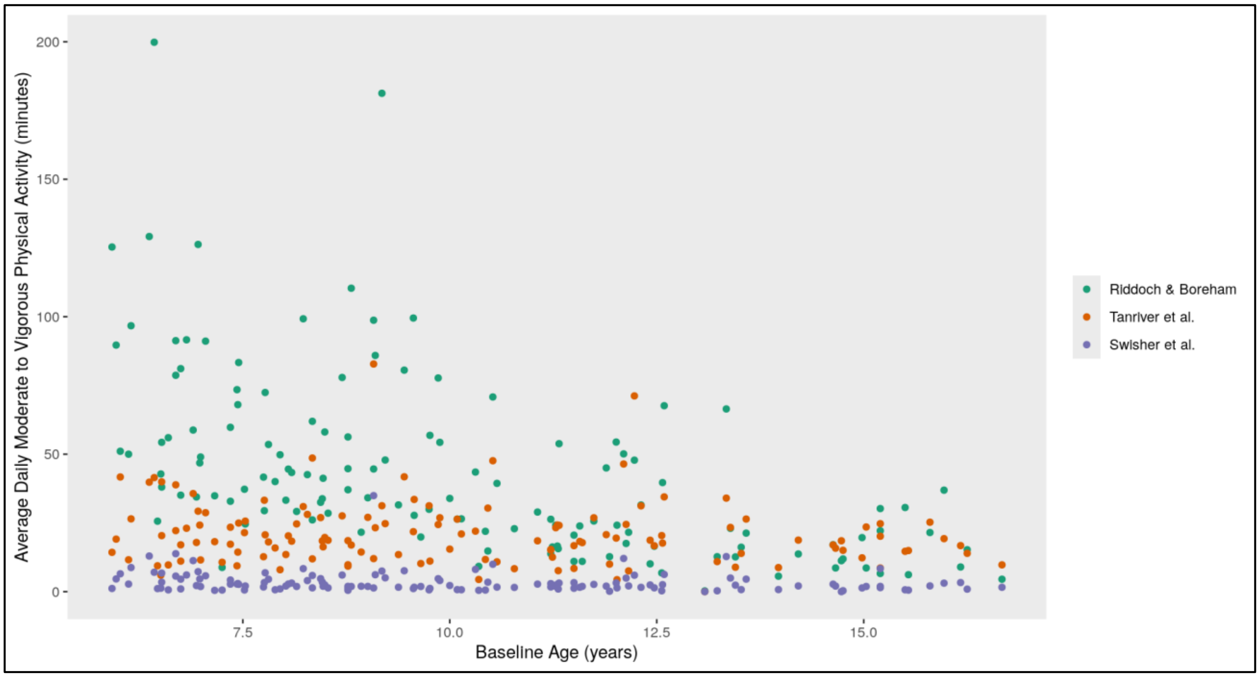


Figure 8 Scatterplot of average daily minutes of moderate to vigorous physical activity against baseline age for the three moderate to vigorous physical activity thresholds for all participants (n=134).

5.3 Association between moderate to vigorous physical activity and FEV_1

Daily cumulative minutes of moderate to vigorous physical activity (exposure) using any of the three thresholds was not statistically significantly associated with daily FEV_1 (percent predicted). The slope coefficients were close to zero and were similar between the crude and adjusted models (Table 6).

Daily data were summarized as categorical variables to reflect low, moderate, and high levels of moderate to vigorous physical activity to understand whether there was a non-linear association (Table 7). For the Riddoch & Boreham and Tanriver et al. thresholds, low was defined as 1 to 30 minutes, moderate as 30 to 60 minutes, and high as 60 or more minutes of moderate to vigorous physical activity per day. The Swisher et al. threshold was broken down into two categories due to low physical activity levels: zero minutes and more than 1 minute of moderate to vigorous physical activity per day. Fizzyo participants with higher levels of moderate to vigorous physical activity had lower levels of FEV_1. On average, individuals in the 120+ minute physical activity category have a decrease of 0.113, 95% CI (-0.176, -0.050) percent predicted, in daily FEV_1 values compared to those in the 0-minute (reference) category, using the Riddoch & Boreham threshold, after adjusting for baseline FEV_1, BMI, age, biological sex and quality of daily ACTs.

The crude and adjusted continuous weekly models (Table 8) showed slopes similar to those of the daily continuous models (Table 6). For Riddoch & Boreham, with every 100-minute increase in weekly moderate to vigorous physical activity, weekly maximum FEV_1 decreases by 0.13 percent predicted, 95% CI (-0.0016, -0.0009), after adjusting for baseline age, BMI, baseline FEV_1, biological sex (male) and ACTs quality, as the reference group.

To understand whether there was a non-linear association, weekly data were summarized as categorical variables to reflect low, moderate and high levels of moderate to vigorous physical activity (Table 9). The weekly categorical moderate to vigorous physical activity and maximum weekly FEV_1 showed a dose-response relationship in the Riddoch & Boreham and Tanriver et al. models. On average, for those in the 60 to 120-minute category, using the Tanriver et al. threshold, relative to those in the 0-minute (baseline) category, weekly maximum FEV_1 decreases by 0.087 percent predicted, 95%CI (-0.454, 0.281), after adjusting for baseline age, BMI, FEV_1, biological sex (male) and ACT quality. The magnitude was small, and the slope was not significantly different from zero.

Table 6 Linear mixed effects regression models presenting the daily continuous moderate to vigorous physical activity slopes and corresponding 95 percent confidence interval, with daily FEV_1 as the outcome variable.

Daily Continuous			
Model	**Riddoch & Boreham, 1995**	**Tanriver et al., 2024**	**Swisher et al., 2015**
Crude	-0.0017 (-0.0021, -0.0014)	-0.0004 (-0.001, 0.0002)	0.0012 (-0.0005, 0.003)
Adjusted	-0.0020 (-0.0023, -0.0017)	-0.0007 (-0.001, 0.0001)	0.0013 (-0.0003, 0.003)

Table 7 Linear mixed effects regression models presenting the daily categorical moderate to vigorous physical activity slopes and corresponding 95 percent confidence interval, with daily FEV_1 as the outcome variable. The Swisher et al. threshold was divided into categories of 0 minutes and 1+ minutes of moderate to vigorous physical activity.

Daily Categorical				
Model	**Categories**	**Riddoch & Boreham, 1995**	**Tanriver et al., 2024**	**Swisher et al., 2015**
Crude	0 Minutes	Ref	Ref	Ref
	Low 1 - 30 Minutes	-0.023 (-0.080, 0.035)	-0.059 (-0.109, -0.008)	-0.038 (-0.072, -0.004)
	Moderate 30 - 60 Minutes	-0.023 (-0.087, 0.041)	-0.067 (-0.127, -0.008)	
	High 60+ Minutes	-0.096 (-0.162, -0.030)	-0.059 (-0.133, 0.016)	
Adjusted	0 Minutes	Ref	Ref	Ref
	Low 1 - 30 Minutes	-0.009 (-0.064, 0.046)	-0.057 (-0.105, -0.009)	-0.034 (-0.066, -0.001)
	Moderate 30 - 60 Minutes	-0.024 (-0.086, 0.037)	-0.086 (-0.143, -0.028)	
	High 60+ Minutes	-0.113 (-0.176, -0.050)	-0.090 (-0.160, -0.018)	

Table 8 Linear mixed effects regression models presenting the weekly continuous moderate to vigorous physical activity slopes and corresponding 95 percent confidence interval, with weekly maximum FEV_1 as the outcome variable.

Weekly Continuous			
Model	**Riddoch & Boreham, 1995**	**Tanriver et al., 2024**	**Swisher et al., 2015**
Crude	-0.0011 (-0.0014, -0.0008)	-0.0013 (-0.0020, -0.0007)	-0.0019 (-0.0038, 0.00005)
Adjusted	-0.0013 (-0.0016, -0.0009)	-0.0015 (-0.0021, -0.0009)	-0.0019 (-0.0038, -0.00004)

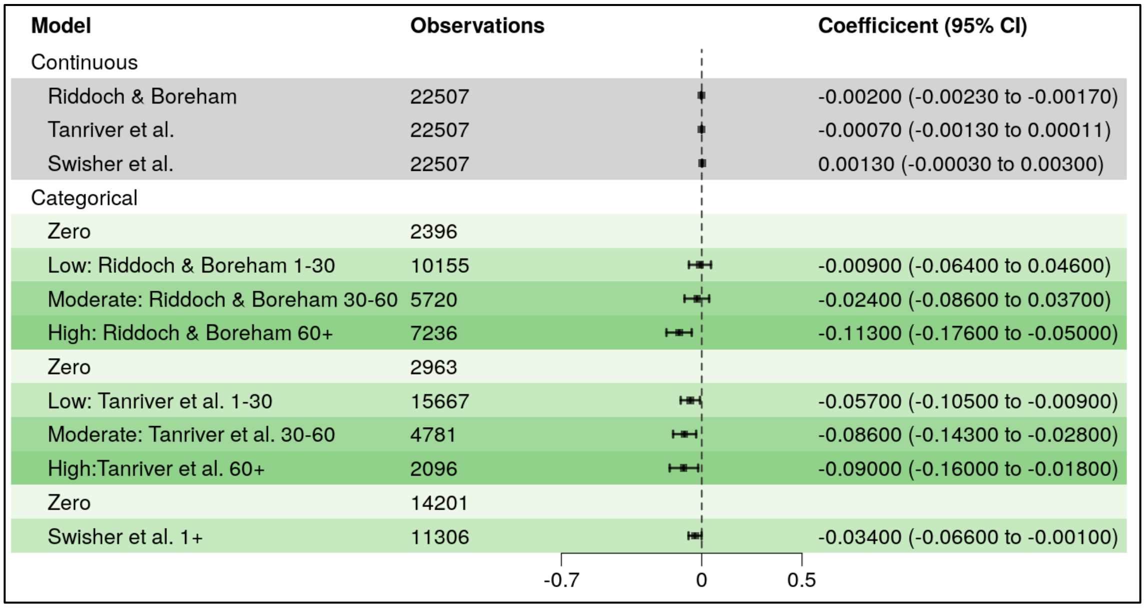
Table 9 Linear mixed effects regression models presenting the weekly categorical moderate to vigorous physical activity slopes and corresponding 95 percent confidence interval, with weekly maximum FEV_1 as the outcome variable. The Swisher et al. threshold was divided into categories of 0 minutes and 1+ minutes of moderate to vigorous physical activity categories

Weekly Categorical				
Model	**Categories**	**Riddoch & Boreham, 1995**	**Tanriver et al., 2024**	**Swisher et al., 2015**
Crude	0 Minutes	Ref	Ref	Ref
	Low 1 – 60 Minutes	-0.142 (-0.546, 0.263)	-0.009 (-0.370, 0.353)	-0.101 (-0.272, 0.070)
	Moderate 60 – 120 Minutes	-0.101 (-0.512, 0.312)	-0.057 (-0.428, 0.315)	
	High 120+ Minutes	-0.227 (-0.626, 0.173)	-0.217 (-0.589, 0.157)	
Adjusted	0 Minutes	Ref	Ref	Ref
	Low 1 – 60 Minutes	-0.125 (-0.524, 0.276)	-0.009 (-0.365, 0.349)	-0.096 (-0.264, 0.074)
	Moderate 60 – 120 Minutes	-0.121 (-0.527, 0.286)	-0.087 (-0.454, 0.281)	
	High 120+ Minutes	-0.259 (-0.654, 0.136)	-0.261 (-0.629, 0.108)	

Forest plots were used to summarize the adjusted daily (Figure 9) and weekly (Figure 10) models. The forest plots visually show that many of the slopes are near zero and how the 95% confidence intervals cross zero and are insignificant.

The daily categories of Tanriver et al. show less dose-response than the daily categories of Riddoch & Boreham. The steps between the category slopes and 95% confidence intervals in Tanriver et al. are very small; these values are also near zero.

The direction and magnitude of the slopes are quite similar between the daily and weekly regression models. The dose-response direction was evident in both daily and weekly models as well; however, the slopes are more negative in the weekly model's highest category.



Model	Observations	Coefficicicent (95% CI)
Continuous		
Riddoch & Boreham	22507	-0.00200 (-0.00230 to -0.00170)
Tanriver et al.	22507	-0.00070 (-0.00130 to 0.00011)
Swisher et al.	22507	0.00130 (-0.00030 to 0.00300)
Categorical		
Zero	2396	
Low: Riddoch & Boreham 1-30	10155	-0.00900 (-0.06400 to 0.04600)
Moderate: Riddoch & Boreham 30-60	5720	-0.02400 (-0.08600 to 0.03700)
High: Riddoch & Boreham 60+	7236	-0.11300 (-0.17600 to -0.05000)
Zero	2963	
Low: Tanriver et al. 1-30	15667	-0.05700 (-0.10500 to -0.00900)
Moderate: Tanriver et al. 30-60	4781	-0.08600 (-0.14300 to -0.02800)
High:Tanriver et al. 60+	2096	-0.09000 (-0.16000 to -0.01800)
Zero	14201	
Swisher et al. 1+	11306	-0.03400 (-0.06600 to -0.00100)

Figure 9 Forest plot comparing the daily continuous and categorical moderate to vigorous physical activity coefficients, 95% confidence intervals, and observations for the adjusted models, with daily FEV1 as the outcome and all covariates included (baseline FEV$_1$, baseline age, baseline BMI, biological sex, and quality of ACT).

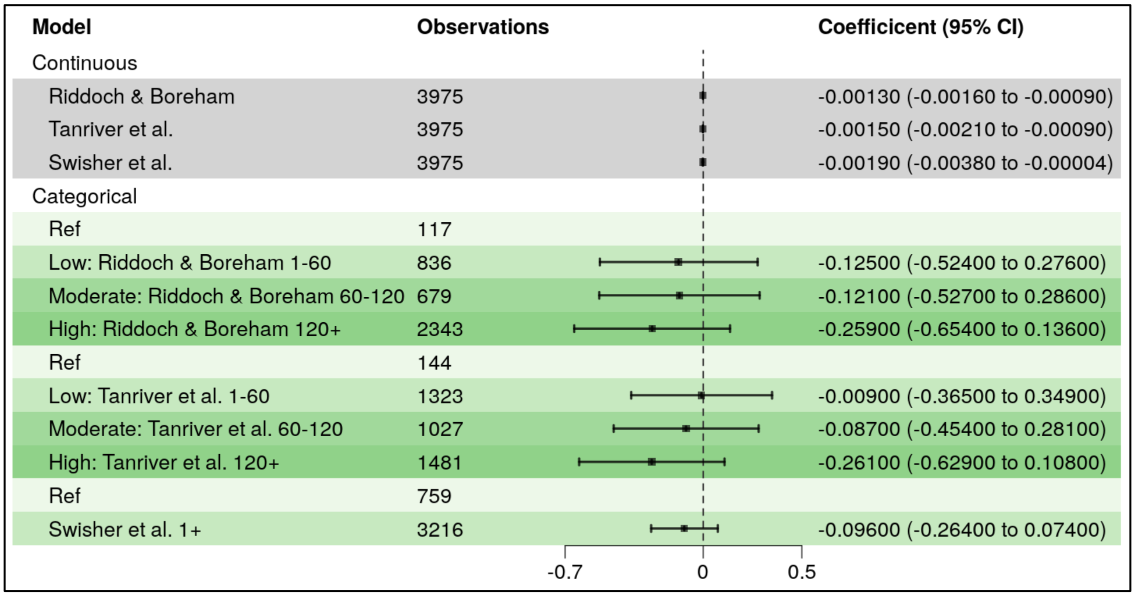


Figure 10 Forest plot comparing the weekly continuous and categorical moderate to vigorous physical activity coefficients and 95% confidence intervals and observations for the adjusted models, with weekly maximum FEV1 as the outcome and all covariates included (baseline FEV$_1$, baseline age, baseline BMI, biological sex, and quality of ACT).

5.4 Verifying Assumptions

The three moderate to vigorous physical activity thresholds produced nearly identical plots when assessing the regression assumptions. As the plots were very similar for all three thresholds, Riddoch & Boreham will present homoscedasticity, Tanriver et al. will present normality, and Swisher et al. will present the dfbeta analysis. All thresholds were investigated to see if each regression assumption was met, and the results were identical across the three thresholds. It was decided to show only one threshold for each assumption to avoid repeating the same information in this section.

To assess homoscedasticity, the residuals from each moderate to vigorous physical activity threshold were plotted against the time variable (days in study) (Figure 11). To meet this assumption, the residuals need to have a random scatter. Figure 11 showed some parabola patterns which do not represent a random scatter. Four participants contributed to these residuals above 2.5 and below -2. These individuals had rather inconsistent daily minutes of moderate to vigorous physical activity and varying FEV_1 values, which ranged from 30 to 105 percent predicted. Once these four participants were removed, Figure 12 showed a more random scatter of residuals around zero. When the regression models were redone, excluding these four participants, the slopes remained insignificant and near zero. Therefore, the removal of the four outliers showed a residual plot that was more closely aligned with the homoscedasticity assumption compared to the plot with all participants.

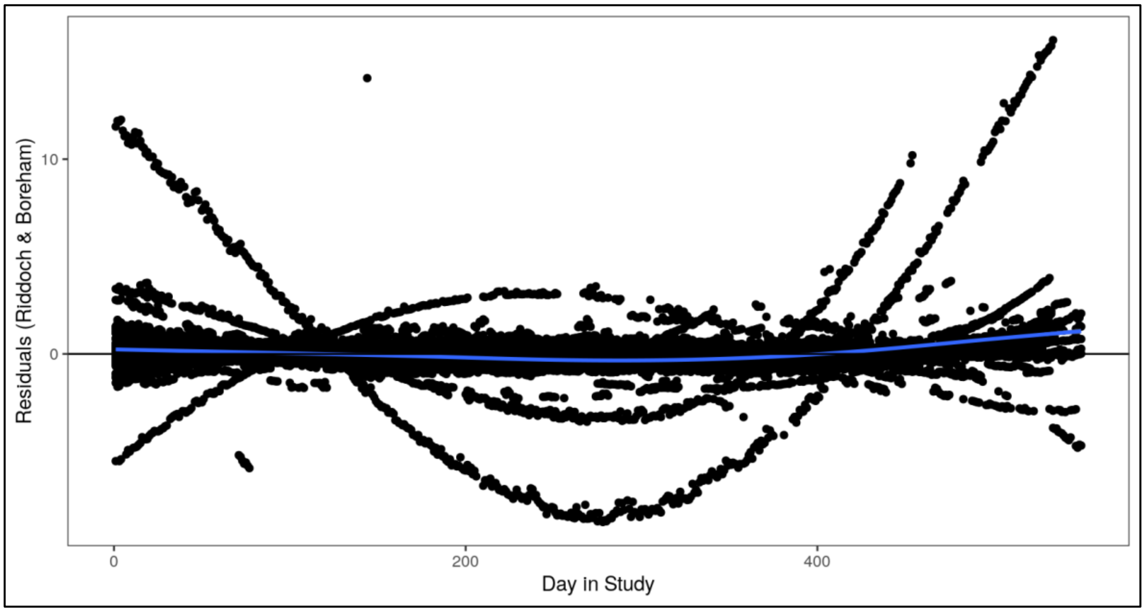


Figure 11 Riddoch & Boreham threshold residuals plotted against the day in study time variable to assess homoscedasticity, including all participants from regression models (n=134).

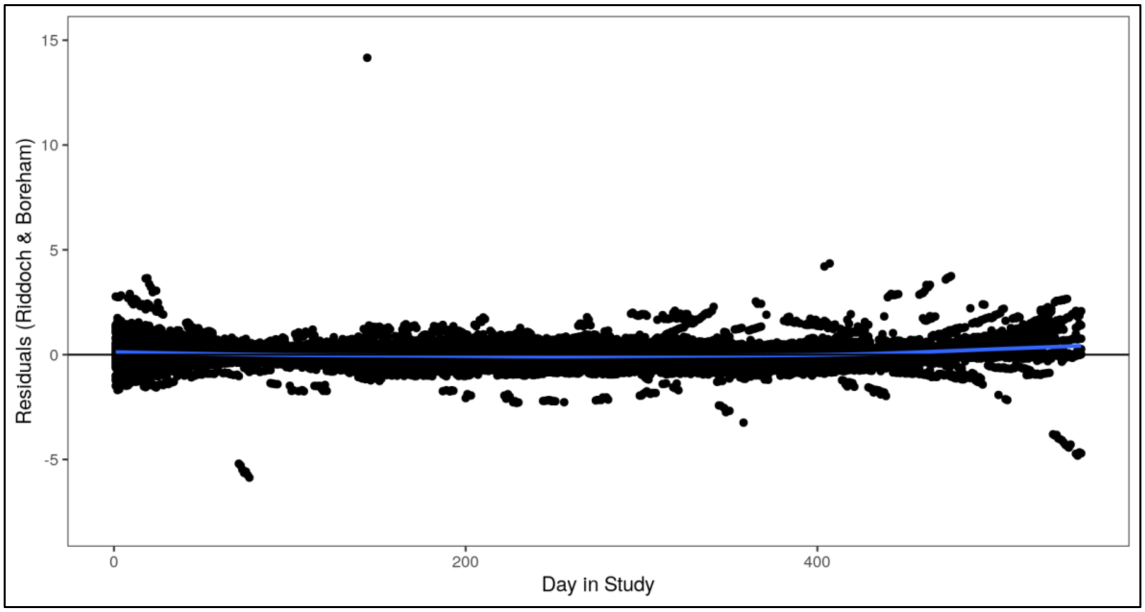


Figure 12 Riddoch & Boreham threshold residuals plotted against the day in study time variable to assess homoscedasticity, with four participants removed due to high residuals (n=130).

Quantile-quantile plots were developed to assess whether the residuals were normally distributed. To meet the assumption, the residuals should follow a straight line. The Tanriver et al. threshold was used to assess the normality assumption, as the three thresholds all showed very similar quantile-quantile plots. Figure 13 shows deviations from the lines around -2.5 and 2.5, which correspond to the same participants who were removed from the homoscedasticity assumption. When the four participants were removed, there were fewer deviations from the line in Figure 14 at high and low residuals. Therefore, removing the four outliers resulted in a plot that aligned more closely with the normality assumption compared to the plot with all participants included.

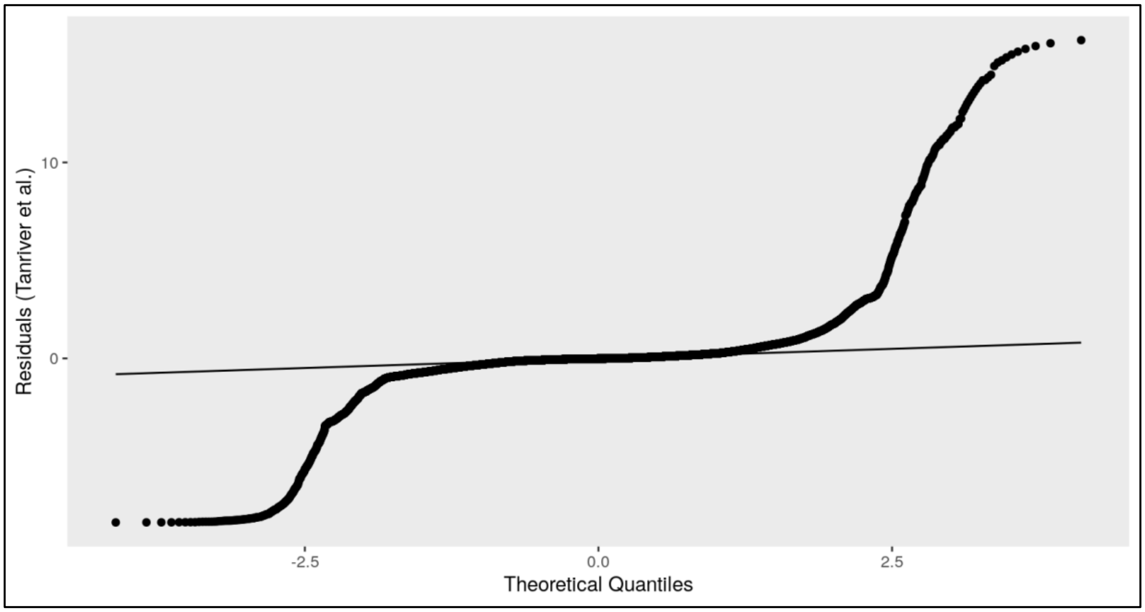


Figure 13 Tanriver et al. residuals plotted against theoretical quantiles to assess if the residuals are normally distributed, including all participants from the regression models (n=134).

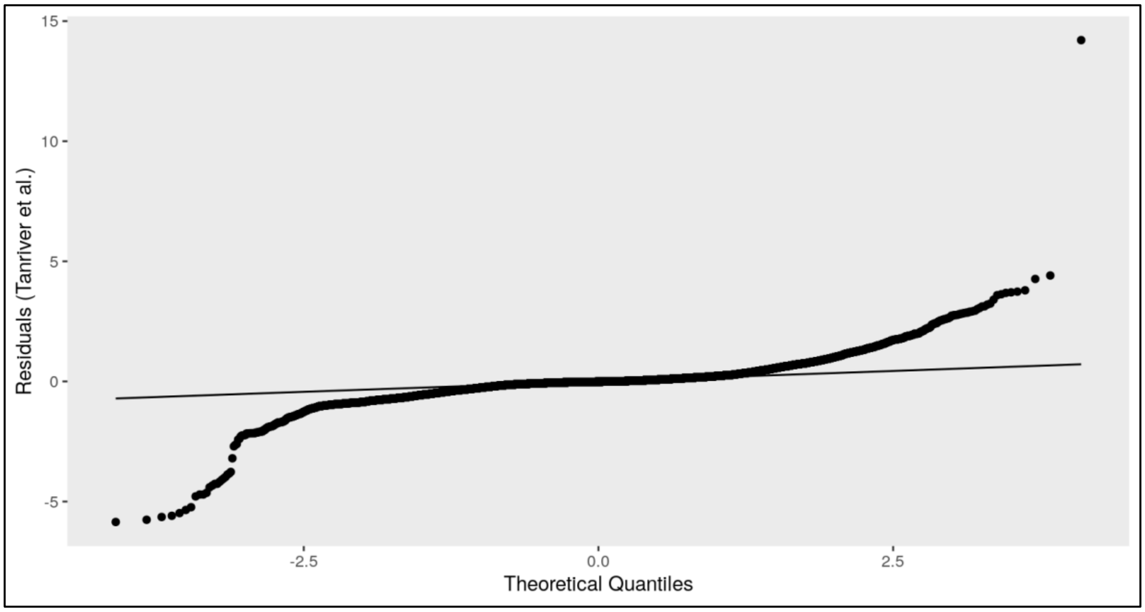


Figure 14 Tanriver et al. residuals plotted against theoretical quantiles to assess if the residuals are normally distributed, excluding participants with high residuals (n=130).

DfBeta analysis was used to identify potential influential outliers. This analysis uses the Swisher et al. threshold because all three physical activity threshold had similar results. Four participants have DfBeta values outside the two dashed lines in Figure 15. The two dashed lines are at -0.1728 and 0.1728, which was determined using $\frac{2}{\sqrt{n}}$. Other than the four points outside the dashed lines, the points have a random scatter around zero. These four points correspond to the four participants with high residuals indicated in the other two assumptions.

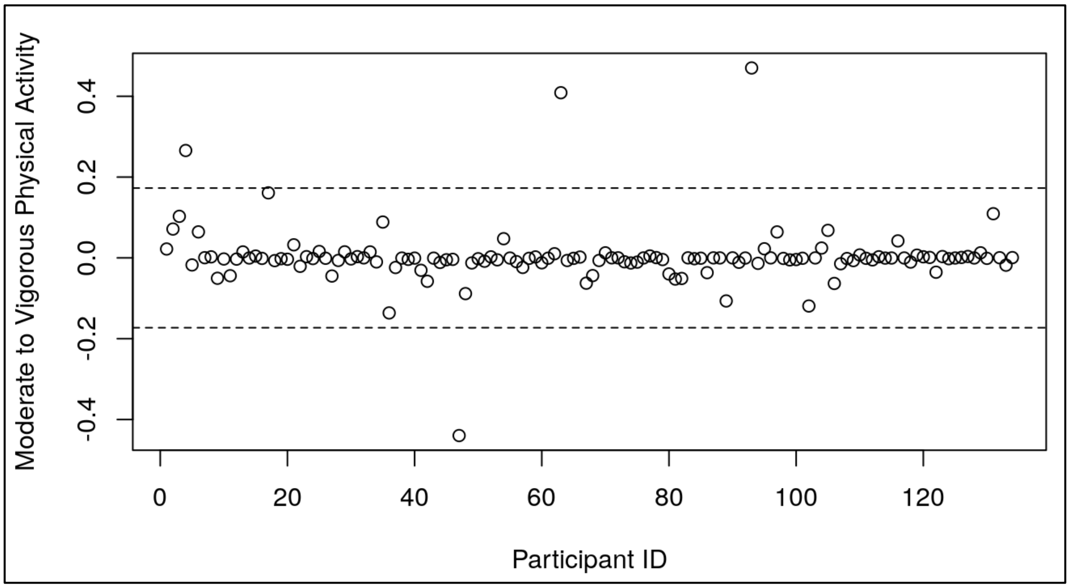


Figure 15 Swisher et al. dfBeta influential points plotted by study email for the main exposure, moderate to vigorous physical activity. All participants from the main analysis (n=134) are included.

5.5 Sensitivity Analysis

The sensitivity analysis limited the days to participants with at least 500 minutes of Fitbit Alta HR wear time. The cut-off of 500 minutes of wear time corresponds to about eight hours daily.

A histogram of the Fitbit Alta HR wear time showed that the distribution was bimodal, and both peaks were included as they were higher than 500 minutes (Figure 16). This cut-off was chosen because 86.3 percent of observations were included in the sensitivity analysis. All participants (n=134) had observations included in the sensitivity analysis.

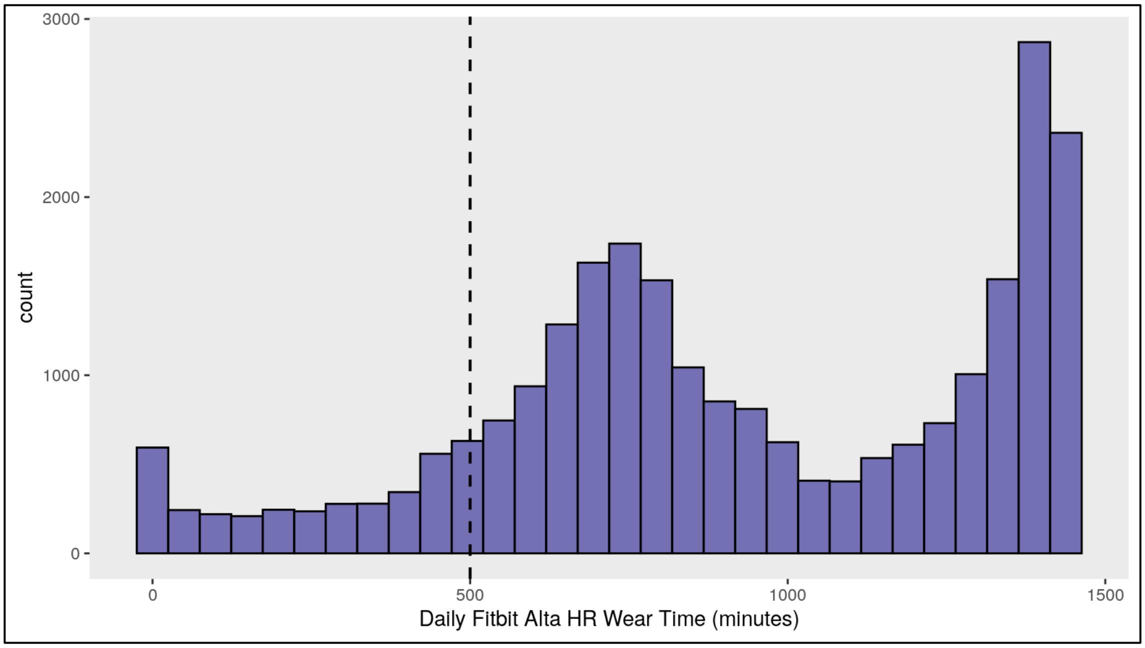


Figure 16 Histogram of daily Fitbit Alta HR wear time in minutes for all participants over 16 months of Project Fizzyo, showing the cut-off for the sensitivity analysis at 500 minutes (21950 observations).

The sensitivity analysis produced near zero coefficients (Table 10), similar to the main analysis that looked at continuous daily and weekly moderate to vigorous physical activity (Table 6 & Table 8). Therefore, the Fitbit Alta HR wear time did not impact the results.

Table 10 Linear mixed effects regression models for days where participants have more than 500 minutes of wear time, presenting the moderate to vigorous physical activity slopes and 95 percent confidence interval, with daily and weekly FEV_1 *as the outcome variable.*

Daily Continuous			
Model	Riddoch & Boreham, 1995	Tanriver et al. 2024	Swisher et al. 2015
Crude	-0.0017 (-0.0021, -0.0014)	-0.00031 (-0.0010, 0.0003)	0.0014 (-0.0004, 0.0032)
Adjusted	-0.0020 (-0.0023, -0.0016)	-0.00005 (-0.0012, 0.00008)	0.0016 (-0.0002, 0.0033)
Weekly Continuous			
Model	Riddoch & Boreham, 1995	Tanriver et al. 2024	Swisher et al. 2015
Crude	-0.0013 (-0.0016, -0.0009)	-0.0016 (-0.0023, -0.0009)	-0.0021(-0.004, -0.000008)
Adjusted	-0.0014 (-0.0017, -0.0010)	-0.0017 (-0.0024, -0.0011)	-0.0021(-0.004, -0.00006)

Chapter 6 Discussion

6.1 Main findings

Objectively measured moderate to vigorous physical activity in children and young people participating in Project Fizzyo was low. For the limited duration and intensity of physical activity observed, neither the total daily nor total weekly minutes of moderate to vigorous physical activity were associated with daily or weekly FEV_1, respectively. The findings were consistent, irrespective of the moderate to vigorous physical activity threshold applied or if moderate to vigorous physical activity was categorized into levels. Even the subset of participants with the highest duration of moderate to vigorous physical activity had similar FEV_1 values to those with lower durations. Since the duration and intensity of physical activity were very low in the study population, the interpretation of the negative associations with FEV_1 is inconclusive.

6.2 Implications

These findings suggest that children and young people with CF may not do very much moderate to vigorous physical activity and that current approaches to define moderate to vigorous physical activity thresholds based on heart rate may be inadequate. The study population had high baseline FEV_1, which may mean they were healthier than the average child with CF. Healthier children may be able to complete more physical activity. A lack of a gold standard heart rate threshold for children makes interpreting estimated physical activity difficult. It is also unclear which of the three thresholds used in this study are correct. Further, the thresholds for moderate to vigorous physical activity were prone to misclassification, limiting the interpretation of the results. With the low estimates of physical activity, the varying methods for defining moderate to vigorous physical activity and varying estimates between thresholds, it is difficult to understand if there is a clinical benefit to FEV_1. Different approaches, such as utilizing a combination of supervised and objective measures of physical activity in a laboratory environment, could be used to establish specific recommendations for the duration and intensity of physical activity for individuals with CF in order to observe improvements in FEV_1. However, this approach has many challenges and may not be directly comparable to a real-world setting and the daily activity patterns of individuals with CF. Future research is needed to objectively define the intensities of physical activity for children to further research the association between physical activity and FEV_1. These results do not suggest that people with CF should stop engaging in physical activity but do suggest that children with CF should continue to do clinically recommended ACTs.

6.3 Strengths

Project Fizzyo addresses all of the previous research gaps, with objective measures of physical activity, over a period of 16 months, with a study population of 145 children. Physical activity data was objectively measured to capture physical activity patterns over 16 months. The sample included in Project Fizzyo (n=145) was larger than other observational studies that utilized objective measures of physical activity. Further, the exposure, outcome, and covariates included in this analysis tried to mitigate the shortcomings of the previous literature.

6.4 Limitations

6.4.1 Exposure Misclassification

Objectively measuring heart rate using the Fitbit Alta HR has advantages over self-reported physical activity but also limitations compared to other objective measures. The Fitbit Alta HR eliminates the need for children or parents to remember specific time intervals or types of physical activity. However, compared to the gold standard electrocardiogram (ECG), all

Fitbits underestimate heart rate and consequently underestimate minutes of moderate to vigorous physical activity (58,81–83). The underestimation is greatest at higher heart rates (58,83). A study by Benedetto et al., 2018 found that Fitbits can underestimate higher heart rates by up to 30 beats per minute (bpm) (83). With the potential underestimation of peak heart rate and minutes of moderate to vigorous physical activity, the association with FEV_1 would attenuate toward the null.

Another aspect that could cause misclassification of moderate to vigorous physical activity was the use of the Polar H10 heart rate monitor to derive peak heart rate and Fitbit Alta HR to measure daily heart rate. In Project Fizzyo, each participant completed a 25-level 10-meter incremental shuttle walk test wearing the Polar H10 heart rate monitor and Fitbit Alta HR (3). Heart rate measurements were similar between the two devices until the participants got closer to their peak heart rate, at which point the Fitbit Alta HR began to sporadically underestimate heart rate, especially when participants were constantly changing direction. Fitbit Alta HR inconsistently measured higher heart rates; in some cases, peak heart rate measurement was accurate, and in others, it was not. Tanriver et al. decided to use the Polar H10 data to derive the peak heart rate equation, which was then used to define the age-specific heart rate threshold for moderate to vigorous physical activity (5). This was a practical decision to give the best possible representation of peak heart rate due to the challenges with the Fitbit Alta HR. While the peak heart rate measurement and Tanriver et al. threshold may have had challenges, there is no gold standard threshold for moderate to vigorous physical activity to compare directly to. Three moderate to vigorous physical activity thresholds were included in this analysis to mitigate the lack of a gold standard activity threshold.

The generalized recommendation from Riddoch & Boreham (PHR >120 bpm), a fixed threshold for achieving moderate to vigorous physical activity, produced higher minutes for participants, especially for younger children. This likely occurred because of the age-dependency of resting and peak heart rates, which decline linearly with age in childhood (66). This could classify individuals into moderate to vigorous physical activity when they are not at this intensity, resulting in measurement bias. The higher estimation of physical activity may bias the association with FEV_1 toward the null and show a weaker but inaccurate association. Tanriver et al., 2024 used an age-specific threshold that, as expected, produced fewer minutes of moderate to vigorous physical activity than Riddoch & Boreham. The threshold from Swisher et al. produced the lowest minutes of activity. The bias could be exacerbated by the Swisher et al. threshold which had a second requirement to be within 70% of peak heart rate. Both Tanriver and Swisher showing low estimates of moderate to vigorous physical activity could have led to a biased association that attenuated towards the null.

Further, it is possible that children did not wear their Fitbit Alta HR and the low physical activity reflects missing data. Participants had days with zero minutes of Fitbit Alta HR wear time due to forgetting to wear it or choosing not to. If these participants forgot to wear their Fitbit Alta HR and did physical activity, it could have caused differential measurement bias. Another reason for missing data was that some participants were not allowed to wear their Fitbit Alta HR during school hours, causing missed activity during physical education classes and lunch breaks. This could cause random measurement bias for all individuals attending these schools. The sensitivity analysis, which limited to participants who wore their Fitbit more than 500 minutes daily for the 16-month project, showed very similar results to the main analysis, and a wear time cut-off did not impact the association between physical activity and FEV_1. It is unclear whether individuals forgot to wear their Fitbit Alta HR while doing physical activity or whether the participants did not complete physical activity and did not wear their Fitbit Alta HR.

As the main exposure variable potentially misclassified moderate to vigorous physical activity, the association with FEV_1 could have been biased toward the null. Despite the potential underestimation of moderate to vigorous physical activity, the observed moderate to vigorous physical activity in the study population would still be low. Compared to the World Health Organization (WHO) guidelines of an average of 60 minutes of moderate to vigorous physical activity daily, the daily median minutes of activity observed in this study were well below this recommendation. Even using the threshold with the highest daily minutes of moderate to vigorous physical activity, the daily median was only half of the daily recommended minutes. In context of the misclassification of physical activity, it is unclear whether the participants did not do moderate to vigorous physical activity, did not wear their Fitbit Alta HR, or whether the thresholds were not appropriate for children.

6.4.2 Outcome Misclassification

Forced expiratory volume in one second (FEV_1) is the primary outcome in CF research. However, it is not clear whether FEV_1 is the most appropriate outcome for physical activity research. Since daily (or weekly) measures of the outcome were not available, a flexible polynomial model was used to extrapolate daily values based on available measures (7). Thus, the daily extrapolated values may be inaccurate measures of the participants' true lung function. It is unclear whether it was appropriate to use the FEV_1 polynomial to extrapolate to daily measures. Some participants in the study had fewer FEV_1 measurements to predict from, and thus, the extrapolated values would have more measurement error. The potential inaccuracy of the polynomial could have biased the extrapolated daily FEV_1 measures and the association with moderate to vigorous physical activity. However, including daily FEV_1 measures was an advantage over previous research that only compared pre- and post-study FEV_1 measures (12,13,15,19,21,24–27,31,36). Daily home spirometry may be a better option to obtain accurate measures of FEV_1 that align with the physical activity measures. One limitation of daily home spirometry is that participants may forget, resulting in missing data. A combination of home spirometry and an FEV_1 polynomial may increase accuracy and mitigate missing data.

There are also more sensitive lung function measures than spirometry. The multiple breath washout test measures the lung clearance index, reflecting global ventilation inhomogeneity and small airway dysfunction (84). A more sensitive outcome measure may be more suitable to detect small improvements in the airways after physical activity. However, multiple breath washout is limited to specialized pulmonary function laboratories and would also be limited by sparse data. Another potential outcome measure could be magnetic resonance imaging (MRI) of the lungs, which would measure ventilation inhomogeneity and a visual representation of lung function changes. However, the high cost of MRI scans may not be feasible for an entire study population over the duration of the study. Other studies have used exercise-focused outcome measures, including cardiopulmonary exercise testing (CPET) and maximum rate of oxygen consumption (VO_2 max), which may closely align with the direct benefits of physical activity. These exercise-focused outcome measures must be measured and interpreted at specialist labs and are burdensome for participants, which may not be feasible for a longitudinal study.

In addition, it is unclear how much exposure (duration, frequency and intensity) is required to observe changes in lung function, if any. The analysis in this study assumes that daily physical activity would impact lung function on the same day, which may not be the case. It may be unrealistic to expect instantaneous improvements in lung function. The addition of a lag time variable for lung function may be necessary for the analysis of moderate to vigorous physical activity and lung function. Therefore, the negative findings observed in this study may also reflect the inadequacy of the outcome to detect changes.

6.4.3 Overall Limitations

Despite Project Fizzyo's strengths, there were notable limitations. Patterns of missingness were observed for the physical activity and lung function data, which were not mitigated in the analyses. Unmeasured confounding factors could influence the association between moderate to vigorous physical activity and FEV_1. Variables such as socioeconomic status, whether the participants were part of sports teams, and participants' diet were not measured. These factors are unlikely to have enough impact to change the interpretation of the main results because the observed moderate to vigorous physical activity was so low.

While Project Fizzyo had quite a large sample size, this study could still be underpowered. The sample size estimate considered observations independent, and the true sample size required to detect a clinically relevant association may be much larger than estimated. Even if the results were statistically significant, the magnitude found was small, negative and not clinically meaningful. The more likely issue was the low observed physical activity (exposure) overall.

6.5 Comparison to Literature

Given the challenges with measuring physical activity and lung function, it is not surprising that there is so much heterogeneity in the literature. The lack of a clinically significant association between physical activity and lung function observed in the two high-quality studies identified (9,10) may also reflect the low observed physical activity and inadequacy of lung function measures taken at two or three points. Twenty-three of the twenty-six studies (88%) in the literature review recorded physical activity that did not meet the WHO recommendations (11–15,17–33,36). Two studies reported habitual physical activity, defined as any activity that is incorporated into daily life (34,35). Activities incorporated into daily life would be at different intensities, and this is not directly comparable to WHO moderate to vigorous physical activity recommendations. Gruber et al. was the only study that reported moderate to vigorous physical activity that met WHO recommendations. The mean (SD) daily moderate to vigorous physical activity was 97.3 (69.9) minutes per day over the 12-month study period. This study defined moderate to vigorous physical activity as three to six metabolic equivalents (METs), measured using ActiGraphs. This study found no association between physical activity and lung function; however, only six participants remained in the 12-month study period and were included in the analysis (16). The participants in the study were all classified as being clinically stable, with a mean (SD) baseline FEV_1 of 102.5 (13.1) percent predicted. This may have caused selection bias, as participants included may have been able to perform higher durations of physical activity compared to individuals with lower baseline FEV_1, which could attenuate the association away from the null.

The high-quality randomized controlled trial by Hebestreit et al., 2022, recorded physical activity that did not meet the WHO recommendations for adults (12). The intervention group in the Hebestriet et al. study was asked to add an additional three hours of vigorous physical activity per week, which would have met the WHO recommendations; however, the adherence in this group was only 56% over the study period. In the only other high-quality study by Elce et al., it was not possible to compare the observed physical activity durations (11). The study reported supervised physical activity in sessions, ranging from two to seven sessions per week in the intervention group. The study by Elce et al. did not equate sessions of physical activity to minutes or hours per day or week. Therefore, it is difficult to compare the physical activity in the study by Elce et al. to the WHO recommendations, which are reported in minutes per day.

The previous literature also used sporadic measures of the outcome (11–15,17–27,29–33,36,74). The study by Elce et al. compared post-exercise lung function but did not adjust for baseline lung function (11). The positive but not clinically significant association between physical activity and FEV_1 could reflect that healthier participants were more likely to exercise. In other studies, measures of lung function were made quarterly (34,35) or, in most cases, at baseline and final assessments (11–15,17–27,29–33,36,74). No studies in the literature review included daily or weekly lung function measures.

In future studies, it will be important to consider the research setting in relation to daily life for children with CF. Supervised physical activity in laboratory settings is advantageous because researchers can accurately measure the intensity of the physical activity; however, the findings may not be generalizable to the real-world setting. Supervised physical activity may allow for the duration, intensity and frequency of physical activity to be defined in which benefits to lung function are observed. A combination of supervised physical activity and objective wrist-worn monitors may be able to provide the data necessary to create physical activity recommendations for children with CF.

Another consideration was that Project Fizzyo and all studies included in the literature review were conducted before the availability of the highly effective modulator therapy for individuals with CF. Studies could be redone to include individuals who use modulator therapies to understand how modulator therapy would affect the association between moderate to vigorous physical activity and FEV_1.

6.6 Knowledge Translation

The main message of this study is that current evidence is inconclusive as to whether moderate to vigorous physical activity improves lung function in children and young people with CF. To date, the study results have been presented at the International Fizzyo Research meetings, Crossroads Research Day, Faculty of Medicine Research Day, and North American CF Conference. A manuscript will be submitted for publication in a medical journal. The results will be shared on social media while partnering with known CF groups such as the CF Trust, Project Fizzyo, and CF Canada.

6.7 Conclusion

Based on the current thresholds for moderate to vigorous physical activity, the observed duration of activity was low in children and young people with CF in Project Fizzyo. Understanding if moderate to vigorous physical activity is associated with better lung function is challenging for several reasons. It remains unclear whether participants were not engaging in moderate to vigorous physical activity, if it was not being captured from the three thresholds, or if it was not the correct intensity to measure. Before the association between moderate to vigorous physical activity and FEV_1 can be further investigated, clearly defined and accurately measured exposure and outcome measures are needed.

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