Journal of Cystic Fibrosis 22 (2023) 31–38

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

journal homepage: www.elsevier.com/locate/jcf

Original Article

Cystic fibrosis related diabetes is not associated with maximal aerobic exercise capacity in cystic fibrosis: a cross-sectional analysis of an international multicenter trial

Thomas Radtke[a,*], Susi Kriemler[a], Lothar Stein[b], Chantal Karila[c], Don S Urquhart[d], David M Orenstein[e], Larry C Lands[f], Christian Schindler[g,h], Ernst Eber[i], Sarah R Haile[a], Helge Hebestreit[j], on behalf of the ACTIVATE-CF Study Working Group[1]

[a] Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich, Switzerland
[b] Hannover Medical School, Institute of Sports Medicine, Hannover, Germany
[c] Service de pneumologie et allergologie pédiatriques - Hôpital Necker Enfants malades – APHP - Université Paris Descartes, Paris, France
[d] Department of Paediatric Respiratory and Sleep Medicine, Royal Hospital for Children and Young People, Edinburgh, UK
[e] Department of Pediatrics, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, USA
[f] Montreal Children's Hospital – McGill University Health, Montreal, QC, Canada
[g] Swiss Tropical and Public Health Institute, University of Basel, Basel, Switzerland
[h] Faculty of Medicine, University of Basel, Basel, Switzerland
[i] Department of Pediatrics and Adolescent Medicine, Medical University of Graz, Graz, Austria
[j] Paediatric Department, University Hospitals Würzburg, Germany

ARTICLE INFO

Article history:
Received 15 April 2022
Revised 24 June 2022
Accepted 27 June 2022
Available online 6 July 2022

Keywords:
Peak oxygen uptake
Cystic fibrosis related diabetes
Physical activity
Dysglycaemia
Exercise capacity

ABSTRACT

Background: Previous studies have reported differences in aerobic exercise capacity, expressed as peak oxygen uptake (VO_{2peak}), between people with and without cystic fibrosis (CF) related diabetes (CFRD). However, none of the studies controlled for the potential influence of physical activity on VO_{2peak}. We investigated associations between CFRD and VO_{2peak} following rigorous control for confounders including objectively measured physical activity.

Methods: Baseline data from the international multicenter trial ACTIVATE-CF with participants ≥12 years performing up to 4 h per week of vigorous physical activity were used for this project. Multivariable models were computed to study associations between CFRD and VO_{2peak} ($mL.min^{-1}$) adjusting for a set of pre-defined covariates: age, sex, weight, forced expiratory volume in 1 s (FEV_1), breathing reserve index, *Pseudomonas aeruginosa* infection, and physical activity (aerobic step counts from pedometry). Variables were selected based on their potential confounding effect on the association between VO_{2peak} and CFRD.

* Corresponding author at: University of Zurich, Hirschengraben 84, 8001 Zurich, Switzerland.
E-mail address: thomas.radtke@uzh.ch (T. Radtke).

[1] Members of the ACTIVATE-CF Study Working Group Ernst Eber, Medical University of Graz, Graz, Austria; Marlies Wagner, Medical University of Graz, Graz, Austria; Helmut Ellemunter, University Hospital Innsbruck, Innsbruck, Austria; Larry C Lands, McGill University Health Centre, Montreal, Quebec, Canada; Nancy Alarie, McGill University Health Centre, Montreal, Quebec, Canada; Chantal Karila, Université Paris Descartes, Paris, France; Clotilde Simon, Unité Recherche Clinique Cochin Necker, Paris, France; Anne Faucou, Unité de Recherche Clinique Cochin Necker, Paris, France; Laurent Mely, Hôpital Renée Sabran, Giens, Hyères, France; Bruno Ravaninjatovo, CHR, Reims, France; Anne Prevotat, CHRU, Hôpital Calmette, Lille, France; Helge Hebestreit, University Hospitals Würzburg, Würzburg, Germany; Jonathan Schaeff, University Hospitals Würzburg, Würzburg, Germany; Lothar Stein, Medical School Hannover, Hannover, Germany; Cordula Koerner-Rettberg, University Children's Hospital of Ruhr University Bochum at St Josef-Hospital, Bochum, Germany; Jutta Hammermann, University Hospital of Dresden, Dresden, Germany; Christina Smaczny, Johann Wolfgang Goethe University, Frankfurt/Main, Germany; Inka Held, CF Zentrum Altona, Hamburg, Germany; Sibylle Junge, Hannover Medical School, Pediatric Pneumology, Allergology and Neonatology, Hannover, Germany; Oliver Nitsche, Johannes Gutenberg-Universität Mainz, Mainz, Germany; Rainald Fischer, Praxis für Lungenheilkunde, München-Pasing, Germany; Jörg Große-Onnebrink, University Hospital Münster, Münster, Germany; Anne Wesner, Klinikum Stuttgart, Olgahospital, Stuttgart, Germany; Andreas Hector, University of Tübingen, Tübingen, Germany; Alexandra Hebestreit, Christiane Herzog-Zentrum, Universitätsklinikum Würzburg, Würzburg, Germany; Susi Kriemler, University of Zurich, Zurich, Switzerland; Christian Schindler, University of Basel, Basel, Switzerland; Thomas Radtke, University of Zurich, Zurich, Switzerland; Christian Benden, University Hospital Zurich, Zurich, Switzerland; Carmen Casaulta, University Children's Hospital Bern, Bern, Switzerland; Reta Fischer, Quartier Bleu, Lindenhospital Bern, Switzerland; Alexander Möller, University Children's Hospital Zurich, Zurich, Switzerland; Erik Hulzebos, University Medical Center Utrecht, Utrecht, The Netherlands; Marcella Burghard, University Medical Center Utrecht, Utrecht, The Netherlands; Don S Urquhart, Royal Hospital for Children and Young People, Edinburgh, UK; Sarah Blacklock, Royal Hospital for Children and Young People, Edinburgh, UK; Debbie Miller, Royal Hospital for Children and Young People, Edinburgh, UK; Zoe Johnstone, Royal Hospital for Children and Young People, Edinburgh, UK; David M Orenstein, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, USA; John D Lowman, University of Alabama at Birmingham, Birmingham, Alabama, USA.

https://doi.org/10.1016/j.jcf.2022.06.012

Results: Among 117 randomized individuals, 103 (52% female) had a maximal exercise test and were included in the analysis. Participants with (n = 19) and without (n = 84) CFRD did not differ in FEV_1, physical activity, nutritional status, and other clinical characteristics. There were also no differences in VO_{2peak} (mL.min^{-1} or mL.kg^{-1}.min^{-1} or% predicted). In the final multivariable model, all pre-defined covariates were significant predictors of VO_{2peak} (mL.min^{-1}), however CFRD [coefficient 82.1, 95% CI -69.5 to 233.8, p = 0.28] was not.
Conclusions: This study suggests no meaningful differences in VO_{2peak} between people with and without CFRD given comparable levels of physical activity.

1. Introduction

Cystic fibrosis-related diabetes (CFRD) is a common comorbidity of cystic fibrosis (CF) lung disease [1] and occurs in up to 50% of adults [2]. The presence of CFRD is associated with an increased risk of infections (e.g., *Pseudomonas aeruginosa*) and exacerbations, weight loss, lung function decline and mortality [1,3–5]. Loss of lung function and nutritional status are the most important complications of CFRD [6], both of which are strong predictors of aerobic exercise capacity in CF [7–11].

Few studies have investigated associations between glucose tolerance and aerobic exercise capacity in people with CF [8,12–14], or used glucose intolerance/CFRD as a covariate in models predicting peak oxygen uptake (VO_{2peak}) [7,15]. In one pediatric study [13], children with CFRD had lower VO_{2peak} compared to individuals with normal glucose tolerance, and in two other studies [8,14] individuals with CFRD or impaired glucose tolerance had lower VO_{2peak} compared to individuals with normal glucose tolerance. In one study in adults, between group differences in VO_{2peak} disappeared after adjustment for lung function [(i.e., forced expiratory volume in 1 s, FEV_1)] [8], a strong and independent predictor of VO_{2peak} [7–11].

CFRD is associated with impairments of several organs including lungs and muscles. Thus, rigorous control for potential confounding factors (i.e., variables that are associated with both the exposure and the outcome) is imperative when studying associations between glucose (in)tolerance and VO_{2peak}, a limitation of previous research [8,12–14]. Various factors may contribute to a lower VO_{2peak} in individuals with CFRD including lung disease severity, nutritional status, *Pseudomonas aeruginosa* infection, physical activity, and others [7,10,16,17]. To the best of our knowledge, the influence of physical activity on the relationship between glucose (in)tolerance and VO_{2peak} has not been addressed in previous studies [8,12–14], the reported lower VO_{2peak} in individuals with CF may be a consequence of lower (habitual) physical activity levels. Moderate intensity aerobic physical activity is recommended for individuals with CFRD [1], however physical inactivity appears to be common among adults with CF showing that only ~1/3 of adults with CFRD are sufficiently physically active and meet the recommendations of ≥150 min of at least moderate intensity activity per week [1,18]. One possible reason for insufficient physical activity among individuals with CF who suffer from CFRD may be the additional burden of blood glucose control and the need for additional carbohydrate intake during prolonged vigorous intensity physical activity [1]. Furthermore, the potential risk of hypoglycemia during prolonged, intense activity [1] could be perceived as relevant additional barrier for regular physical activity and subsequently impact on a person's aerobic exercise capacity in the long-term.

The aim of this study was to explore the relationship between CFRD and VO_{2peak} in an international cohort of adolescents and adults with CF following rigorous control for potential confounders including objectively measured physical activity.

2. Methods

For the purpose of this study, we analyzed baseline data from the ACTIVATE-CF trial, an international multicenter randomized controlled trial conducted between June 2014 and March 2016 [19]. The study design, endpoints and measurements have been described in detail elsewhere [20]. In brief, two baseline study visits (within 14–28 days) were conducted prior to random allocation of study participants into either a physical activity intervention or control group (usual care). Baseline visits included assessment of clinical status, pulmonary function and cardiopulmonary exercise testing (CPET), oral glucose tolerance test (OGTT), and physical activity [20]. At all sites, assessments were performed according to study-specific standard operating procedures.

2.1. Cardiopulmonary exercise testing

In all centers, cardiopulmonary exercise testing (CPET) was performed on a cycle ergometer. The protocol consisted of a 3-min resting phase, a 3-min unloaded phase at minimal workload (warm-up), a linear minute-by minute increment in work rate, and a 3-min recovery phase. The work rate increments were chosen based on the subject's height: <120 cm (10 Watt); 120–150 cm (15 Watt) and >150 cm (20 Watt) [21]. A maximal effort during CPET was defined as: 1) plateau in VO_2 despite a further increase in work rate; 2) a respiratory exchange ratio (RER) >1.05; 3) a peak heart rate that reached or exceeded predicted peak heart rate (for children ≥195 beats.min^{-1}, for adults based on published equations); 4) a minute ventilation at peak exercise (V_{Epeak}) ≥ 85% of estimated maximal voluntary ventilation (MVV= FEV_1 x 40); 5) achievement of predicted VO_{2peak} [22]; or 6) predicted peak work rate ($Watt_{peak}$) [23]. At least one of six criteria had to be fulfilled for the test to be considered maximal. Percent predicted values for VO_{2peak} [22] and $Watt_{peak}$ [24] were calculated.

2.2. Pulmonary function testing

Spirometry and body plethysmography were performed according to European Respiratory Society and American Respiratory Society standards [25,26]. All tests were performed prebronchodilation. Percent predicted values and z-scores were computed for FEV_1 and forced vital capacity (FVC) [27]. The ratio of residual volume (RV) to total lung capacity (TLC) was used to assess the degree of air trapping.

2.3. Oral glucose tolerance test (OGTT)

In all individuals without an established diagnosis of CFRD at study entry (n = 98), an OGTT was performed after an 8 h fast according to standards of the American Diabetes Association [1]. Subjects drank a standard beverage containing 1.75 g glucose per kg bodyweight (maximum 75 g) dissolved in water, and

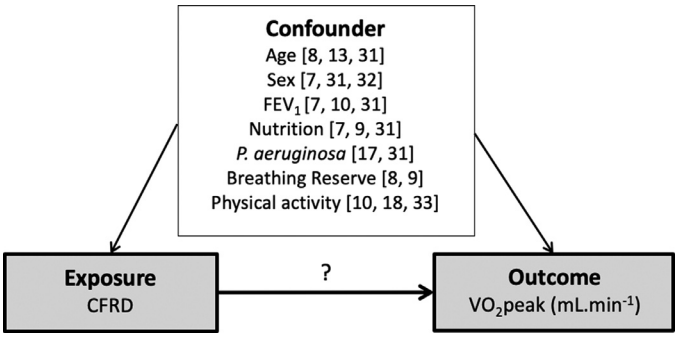

Fig. 1. Directed acyclic graph displaying the exposure – outcome association between cystic fibrosis related diabetes (exposure) and peak oxygen uptake (VO_{2peak}, outcome) and the role of potential confounders. The selection of confounders was done based on content knowledge and available evidence from previous research (i.e., references are given in brackets). Herein, a confounder is defined as a variable that is associated with both the exposure and outcome, and does not reside in the causal pathway between the exposure and outcome of interest [28,29]. CFRD, cystic fibrosis related diabetes; FEV_1, forced expiratory volume in 1s: *P. aeruginosa, Pseudomonas aeruginosa*.

blood samples were taken before and after 1 and 2 h, respectively. We defined impaired glucose tolerance as fasting glucose $\geq$6.3 mmol.L^{-1} or if 2 h plasma glucose was 7.8–11.0 mmol.L^{-1} [1,8,14].

2.4. Physical activity

We measured physical activity with a triaxial pedometer (Omron HJ-322 U-E) for seven consecutive days between the first and second baseline study visit. The device was initialized for each subject during the first study visit including the measurement of individual stride length. The total number of daily steps and aerobic exercise steps were extracted from the pedometer at the second study visit. Aerobic steps are counted by the device when a person walks more than 60 steps per minute for more than 10 consecutive minutes.

2.5. Development of statistical model and justification of covariates

We developed a theoretical and conceptual framework through a review of previous research to visualize causal links between exposure (CFRD) and outcome (VO_2peak) [28–30], see Fig. 1. We drew directed acyclic graphs (DAGs, also known as causal diagrams) to conceptualize our assumptions about the data analysis process, and aiming to identify potential confounders (covariates) to be adjusted for in our multivariable models based on content knowledge and available evidence from previous research [28–30]. Herein, a potential confounder is defined as a variable that is associated with both the exposure and the outcome of interest, and does not reside in the causal pathway between the exposure and outcome of interest [28,29]. We decided to present a simplified version of a DAG (Fig. 1) excluding unmeasured variables (e.g., vascular function), variables that do not fulfill the criterion for a confounder according to our approach (e.g., pancreatic insufficiency), colliders (i.e., a variable that is influenced by two other variables), and mediators.

The primary outcome of this study was VO_{2peak} expressed as mL.min^{-1}. The basic model for CFRD (yes, no) included the covariates age [8,13,31], sex [7,31,32], nutritional status (weight) [7,9,31] and FEV_1 z-score [7,10,31], all of which are known to be associated with CFRD, but also associated with VO_2peak. In addition, *Pseudomonas aeruginosa* infection [17,31], breathing reserve index (V_{Epeak}/MVV_{pred}) [8,9], and physical activity (i.e., total number of steps and aerobic steps were tested as separate variables in the model) [10,18,33] were added to the model. While there is clear evidence that people with a 'severe' genotype (e.g., a genotype commonly associated with pancreatic insufficiency) are more likely to develop CFRD [4,31,32], conflicting data on the association between CF transmembrane conductance regulator (CTFR) genotype class and VO_{2peak} exist [7,34]. We decided not to include *CFTR* genotype in the multivariate model to predict VO_{2peak} due to the small number of people with CFRD in our cohort, and the fact that there is substantial variation in clinical status among individuals with the same *CFTR* genotype. For the descriptive analysis, we categorized *CFTR* genotype into three groups: 1) F508del homozygous, 2) F508del heterozygous, and 3) non-F508del mutation [35].

In addition, we performed regression analysis using a multiplicative, allometric approach [7,10,36] to better adjust for potential effects of body size and lung function on the relationship between CFRD and VO_{2peak}. Allometric scaling assumes that VO_{2peak} is not linearly related to measures of body size, for example body mass M, but is proportional to power functions of those measures, for example M to the power of an exponent x. This approach has been used previously to determine predictors of VO_{2peak} in people with cystic fibrosis [7,10]. For the allometric model, we computed the natural logarithm of VO_{2peak} (dependent variable) and added the same covariates determined by the primary model into the allometric model, using the natural logarithm of all measures of body size in the model while all other variables entered were unchanged.

2.6. Statistical analysis

Participants' characteristics are presented as median (interquartile ranges) or numbers (percentages). Baseline characteristics between groups (i.e., CFRD versus no CFRD or impaired glucose tolerance/CFRD versus normal glucose tolerance) were compared using the non-parametric Wilcoxon rank sum test or the Chi-square test, as appropriate. We report mean values from both baseline visits for all pulmonary function tests (i.e., FEV_1, FVC, and RV/TLC).

Multilevel linear mixed effect regression models were used to analyze associations between CFRD and VO_{2peak} adjusted for covariates discussed before (see Fig. 1) including study center as a random effect. Bayesian information criterion (BIC) was used to select a best fit model containing at least CFRD, age, sex, weight, and FEV_1, and choosing between a) step count, aerobic step count or no step count, b) V_{Epeak}/MVV_{pred} included or not included, and c) *Pseudomonas aeruginosa* included or not included ($3 \times 2 \times 2 = 12$ total models). The model with lowest BIC was that containing aerobic step count, VE_{peak}/MVV_{pred} and *Pseudomonas aeruginosa*, regardless of which VO_{2peak} units were used as the outcome. After model selection, step counter data (8 (12) missing values for total (aerobic) step count) were imputed by using multiple imputations by chained equations (20 imputations). The complete case models were then refit using the imputed data, and pooled results reported. In addition, we run the same regression model comparing the group of participants with normal glucose tolerance compared to a group of participants with impaired glucose tolerance and CFRD.

3. Results

One-hundred and seventeen individuals completed the two baseline visits and were randomized within the ACTIVATE-CF trial [19]. Among those, 110 participants performed a maximal exercise test with measurement of expired gasses and 5 individuals without measurements of expired gasses, respectively. Valid maximal exercise tests including VO_{2peak} and peak work rate (W_{peak}) values or W_{peak} only were available for 100 and 103 subjects, respectively.

Table 1
Participants' clinical characteristics according to diabetic status.

	All (n = 103)	Participants without CFRD (n = 84)	Participants with CFRD (n = 19)	p-value
Age (years)	20 (16, 27)	19 (15, 26)	24 (19, 32)	0.07
Sex, n (% female)	54 (52)	43 (51)	11 (58)	0.60
***CFTR* genotype**				
F508del homozygous, n (%)	48 (47)	39 (46)	9 (47)	>0.99
F508del heterozygous, n (%)	39 (38)	32 (38)	7 (37)	
Other, n (%)	16 (16)	13 (15)	3 (16)	
Clinical status				
P. aeruginosa infection, n (%)	57 (55)	45 (54)	12 (63)	0.45
BMI z-score	−0.29 (−0.85, 0.70)	−0.26 (−0.86, 0.75)	−0.43 (−0.70, 0.59)	0.79
Ivacaftor, n (%)	4 (4)	4 (5)	0 (0)	1.000
Orkambi, n (%)	6 (6)	5 (6)	1 (5)	0.691
Oral glucose tolerance test*				
Fasting plasma glucose (mmol.L^{-1})	–	5.20 (4.80, 5.60)	–	–
2-h plasma glucose (mmol.L^{-1})	–	6.11 (4.97, 7.90)	–	–
CFRD medication				
Insulin, n (%)	–	–	13 (68.4)	
Oral hypoglycemic therapy, n (%)	–	–	3 (15.8)	
No treatment, n (%)			3 (15.8)	
Pulmonary function				
FEV_1 (% predicted)	79 (56, 89)	80 (57, 89)	62 (49, 84)	0.19
FEV_1 z-score	−1.79 (−3.58, −0.89)	−1.71 (−3.30, −0.85)	−3.01 (−3.99, −1.28)	0.14
FVC (% predicted)	88 (76, 100)	88 (78, 101)	81 (70, 94)	0.18
FVC z-score	−0.98 (−2.08, −0.07)	−0.94 (−1.77, 0.07)	−1.28 (−2.52, −0.62)	0.15
RV- /TLC**	0.34 (0.28, 0.46)	0.33 (0.28, 0.46)	0.37 (0.29, 0.51)	0.41

Data are median (interquartile range, IQR) or number (percentage). BMI, body mass index; CFRD, cystic fibrosis related diabetes; CFTR, cystic fibrosis transmembrane conductance regulator; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity. Comparisons between groups were done using the non-parametric Mann-Whitney-U test or Chi-square test, as appropriate. *The oral glucose tolerance test was not performed in individuals with an established diagnosis of CFRD. ** RV/TLC: 8 missing values in group without CFRD.

Table 2
Cardiopulmonary exercise testing and physical activity data for individuals with and without cystic fibrosis related diabetes.

	All (n = 103)	Participants without CFRD (n = 84)	Participants with CFRD (n = 19)	p-value
Cardiopulmonary exercise test				
Wpeak (Watt.kg^{-1})	2.63 (2.07, 3.17)	2.69 (2.12, 3.22)	2.53 (2.05, 2.96)	0.46
Wpeak (% predicted)	87 (79, 101)	88 (79, 102)	87 (79, 96)	0.52
VO_{2peak} (mL.min^{-1})	1832 (1495, 2237)	1838 (1524, 2233)	1830 (1402, 2305)	0.72
VO_{2peak} (mL.kg^{-1}.min^{-1})	32.4 (27.7, 39.2)	33.0 (27.6, 39.6)	30.8 (27.7, 36.3)	0.53
VO_{2peak} (% predicted)	75 (66, 89)	74 (66, 89)	76 (64, 88)	0.71
Peak O_2-pulse (mL.$beat^{-1}$)	10.1 (8.7, 12.9)	10.1 (8.9, 12.8)	9.5 (8.0, 13.1)	0.59
VE_{peak}/MVV_{pred} (%)	76 (63, 90)	74 (63, 88)	80 (67, 96)	0.15
RER	1.18 (1.11, 1.26)	1.18 (1.10, 1.26)	1.19 (1.16, 1.24)	0.50
HR_{peak} (beats.min^{-1})	180 (168, 187)	181 (168, 187)	177 (168, 188)	0.86
SpO_2min (%)	96 (93, 98)	96 (94, 98)	94 (92, 96)	0.048
Physical activity				
No structured PA, n (%)*	13 (12.6)	9 (10.7)	4 (21.1)	0.22
Vigorous PA (hours.$week^{-1}$)*	1.25 (0.50, 2.12)	1.25 (0.69, 2.25)	1.25 (0.50, 1.50)	0.37
Step counts (n)**	5570 (3867, 7563)	5967 (3908, 7730)	4629 (3697, 6123)	0.23
Aerobic step counts (n) **	664 (0, 1486)	773 (37, 1406)	492 (0, 2190)	0.98

Data are median (interquartile range, IQR) or number (percentage). HR, heart rate; MVV, maximum voluntary ventilation; O_2, oxygen; PA, physical activity; RER; respiratory exchange ratio; SpO_2, oxygen saturation; VE_{peak}; peak minute ventilation; VO_2peak, peak oxygen consumption; Wpeak, peak power output. Comparisons between groups were done using the non-parametric Mann-Whitney-U test. *Physical activity history was assessed at the baseline visit. Vigorous physical activity (hours.$week^{-1}$) was assessed with a self-administered questionnaire and the participant's information was re-evaluated in an interview with the study staff at each site. **Data on step counts/aerobic step counts were available for 78/74 individuals without CFRD and 17/17 individuals with CFRD (total n = 95/91). Missing data were imputed for the statistical models, see statistical analysis section.

There were no differences in anthropometric characteristics, pulmonary function, and physical activity between those with CFRD compared to those without CFRD (Tables 1 and 2). None of the diabetic participants experienced a hypoglycemic event during CPET or reported such events during physical activities as part of the 12-months ACTIVATE-CF trial, except one individual at night following excessive exercise (3 h) in combination with inadequate food intake. Among the diabetic group (n = 19), 5 (26.3%) reported breathlessness during physical activities, but none of them reported on hypoglycemic events. Altogether, participants had reduced aerobic exercise capacity, but no differences were observed in CPET-related outcomes between individuals with CFRD compared to those without CFRD (see Table 2), except a lower oxygen saturation at peak exercise in those with CFRD (Table 2). Further, in unadjusted analyses, no differences were noted in clinical characteristics, pulmonary function, CPET data and self-reported and objectively measured physical activity between individuals with normal versus impaired glucose tolerance versus CFRD, except for differences in oxygen pulse at peak exercise among groups (Table 3). Comparable results were found when participants with impaired glucose tolerance and CFRD were combined in one group (n = 40) and compared to a group of individuals with normal glucose tolerance (n = 63), see **Table S1**. Of note, the group of individuals with impaired glucose tolerance and CFRD had a higher propor-

Table 3
Comparison of clinical characteristics, lung function, aerobic exercise capacity and physical activity between individuals with normal glucose tolerance, impaired glucose tolerance and cystic fibrosis related diabetes.

	Normal glucose tolerance (n = 63)	Impaired glucose tolerance (n = 21)	CFRD (n = 19)	p-value
Age (years)	20 (15, 26)	18 (16, 24)	24 (19, 32)	0.13
Sex, n (% female)	28 (44)	15 (71)	11 (58)	0.087
***CFTR* genotype**				
F508del homozygous, n (%)	27 (43)	12 (57)	9 (47)	0.85
F508del heterozygous, n (%)	25 (40)	7 (33)	7 (37)	
Other	11 (17)	2 (9.5)	3 (16)	
Clinical status				
P. aeruginosa infection, n (%)	35 (55.6)	10 (47.6)	12 (63.2)	0.61
BMI z-score	−0.25 (−0.86, 0.79)	−0.29 (−0.84, 0.30)	−0.43 (−0.70, 0.59)	0.96
Ivacaftor, n (%)	2 (3.2)	1 (4.8)	0 (0)	0.99
Orkambi, n (%)	4 (7.7)	1 (5.6)	1 (6.2)	0.99
Oral glucose tolerance test*				
Fasting plasma glucose (mmol.L^{-1})	5.20 (4.70, 5.50)	5.27 (5.05, 5.66)	–	0.19
2-h plasma glucose (mmol.L^{-1})	5.57 (4.55, 6.27)	8.50 (8.10, 9.21)	–	<0.001
Lung function				
FEV_1 (% predicted)	80 (55, 89)	80 (63, 91)	62 (49, 86)	0.39
FEV_1 z-score	−1.71 (−3.62, −0.94)	−1.89 (−2.78, −0.76)	−3.01 (−3.99, −1.28)	0.40
FVC (% predicted)	88 (79, 99)	87 (77, 102)	81 (68, 95)	0.36
FVC z-score	−0.95 (−1.93, −0.08)	−0.90 (−1.65, 0.13)	−1.28 (−2.52, −0.62)	0.29
RV- /TLC	0.33 (0.27, 0.47)	0.34 (0.30, 0.44)	0.37 (0.29, 0.48)	0.70
Cardiopulmonary exercise test				
Wpeak (Watt.kg^{-1})	2.69 (2.19, 3.22)	2.69 (1.97, 3.20)	2.53 (2.05, 2.96)	0.75
Wpeak (% predicted)	85 (77, 100)	98 (83, 109)	87 (79, 96)	0.31
VO_{2peak} (mL.min^{-1})	1944 (1517, 2394)	1668 (1540, 1803)	1830 (1402, 2305)	0.12
VO_{2peak} (mL.kg^{-1}.min^{-1})	33.11 (28.62, 39.22)	32.94 (26.03, 40.37)	30.81 (28.32, 35.63)	0.78
VO_{2peak} (% predicted)	74 (65, 86)	80 (70, 95)	76 (64, 88)	0.50
Peak O_2-pulse (mL.$beat^{-1}$)	10.8 (8.9, 13.2)	9.4 (8.2, 10.2)	9.5 (7.9, 13.2)	0.048
VE_{peak}/MVV_{pred} (%)	75 (62, 88)	72 (65, 86)	80 (67, 96)	0.34
RER	1.18 (1.09, 1.28)	1.18 (1.14, 1.23)	1.19 (1.16, 1.24)	0.77
HR_{peak} (beats.min^{-1})	181 (168, 187)	181 (170, 189)	177 (168, 188)	0.79
SpO_2min (%)	96 (93, 98)	97 (95, 98)	94 (92, 96)	0.095
Physical activity				
Vigorous PA (hours.$week^{-1}$)	1.25 (0.62, 2.50)	1.12 (0.75, 2.00)	1.25 (0.50, 1.50)	0.59
Step counts (n)	6135 (3908, 7828)	5369 (3866, 7239)	4629 (3697, 6123)	0.36
Aerobic step counts (n)	890 (37, 1396)	483 (115, 1662)	492 (0, 2109)	0.99

Data are median (interquartile range, IQR) or number (percentage). BMI, body mass index; CFRD, cystic fibrosis-related diabetes; CFTR, Cystic fibrosis transmembrane conductance regulator; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; MVV, maximum voluntary ventilation; O_2, oxygen; PA, physical activity; RER; respiratory exchange ratio; RV, residual volume; SpO_2, oxygen saturation; TLC, total lung capacity; VE_{peak}; peak minute ventilation; VO_2peak, peak oxygen consumption; Wpeak, peak power output. Comparisons between groups the three groups were done using the non-parametric Kruskal-Wallis test (i.e., comparison between fasting plasma glucose and 2-hour plasma glucose between the groups with normal and impaired glucose tolerance). *The oral glucose tolerance test was not performed in individuals with an established diagnosis of CFRD. ** Vigorous physical activity (hours.$week^{-1}$) was assessed with a self-administered questionnaire and the participant's information was re-evaluated in an interview with the study staff at each site.

tion of females which may explain the differences in peak oxygen pulse (**Table S2**). Table 4 shows the results of the two regression models with imputed data. In the final multivariable models, CFRD was not a significant predictor of VO_{2peak} (mL.min^{-1}). Aerobic step count had a better model fit than total number of daily steps and was selected as covariate for the final model. The allometric model (ln VO_{2peak}) confirmed our basic model (Table 4). The results of the two regression models were comparable; all pre-defined covariates were significant predictors of VO_{2peak} except *Pseudomonas aeruginosa* infection in the allometric model, but CFRD showed no evidence of an association with VO_{2peak}. Complete case models for VO_{2peak} and lnVO_{2peak} (i.e., without imputed data) are given **Table S2** in the online supplementary material. The models comparing individuals with normal glucose tolerance with those with impaired glucose tolerance and CFRD revealed similar results, except that *Pseudomonas aeruginosa* infection was no longer a predictor of VO_{2peak} in the allometric model (**Table S3**).

4. Discussion

This study investigated the association between CFRD and maximal aerobic exercise capacity in an international cohort of adolescents and adults with a broad range of CF lung disease severity. In univariate analyses, we found no differences in VO_{2peak} (primary endpoint) and other CPET-related outcomes between individuals with and without CFRD. In multivariable models including a set of pre-defined covariates, CFRD was not associated with VO_{2peak}.

To our knowledge, this is the first comprehensive study investigating associations between CFRD and VO_{2peak} following rigorous control for potential confounders. In univariate analyses, no differences were observed in VO_{2peak} and other CPET-related parameters between individuals with or without CFRD, and between groups of individuals with normal glucose tolerance, impaired glucose tolerance, and CFRD. The latter finding is in contrast to previous single-center studies (sample size between 46 and 84 participants) reporting differences in VO_{2peak} between children with normal glucose tolerance compared to those with CFRD [13], and children and adults with normal glucose tolerance compared to those with impaired glucose tolerance or CFRD [8,14]. Some studies included a selection of covariates into their multivariate analysis [8,13], but none included *Pseudomonas aeruginosa* infection and physical activity, known determinants of VO_{2peak} [10,17,33] and plausible associates of CFRD [31]. In our multivariable models, CFRD was not a significant predictor of VO_{2peak}. Our findings are consistent with the largest study (n = 726) to date investigating predictors of VO_{2peak}. In this analysis, CFRD was not a significant predictor in a

Table 4
Multivariable models on the association between cystic fibrosis related diabetes and maximal aerobic exercise capacity.

	Coefficients	95% CI
VO_{2peak} (mL.min^{-1})		
Age (years)	−17.7	−25.6 to −9.9
Female sex	−517.0	−653.8 to −380.1
Weight (kg)	20.2	14.4 to 26.0
FEV_1 (z-score)	119.3	67.9 to 170.8
P. aeruginosa infection	−171.4	−173.7 to −25.2
VE_{peak}/MVV_{pred}	6.4	1.6 to 11.3
Aerobic steps (steps.day^{-1})*	23.1	3.1 to 43.2
CFRD	82.1	−69.5 to 233.8
ln VO_{2peak} (mL.min^{-1})		
Age (years)	−0.006	−0.009 to −0.002
Female sex	−0.192	−0.254 to −0.130
ln weight (kg)	0.331	0.148 to 0.515
ln FEV_1 (z-score)	0.491	0.360 to 0.623
P. aeruginosa infection	−0.045	−0.109 to 0.019
ln VE_{peak}/MVV_{pred}	0.302	0.147 to 0.457
ln Aerobic steps (steps.day^{-1})*	0.018	0.008 to 0.027
CFRD	0.030	−0.038 to 0.097

CFRD, Cystic Fibrosis related diabetes; FEV_1, forced expiratory volume in one second; *P. aeruginosa, Pseudomonas aeruginosa.* VE_{peak}/MVV_{pred}, peak ventilation/predicted maximum voluntary ventilation; VO_{2peak}, peak oxygen uptake. The categorical variables CFRD and *Pseudomonas aeruginosa* infection are coded as '0′ = no; '1′ = yes. Sex is coded as '0′ for females and '1′ for males. Ln, natural logarithm. *Coefficients for aerobic step counts are shown per additional 500 steps. All models included a random intercept for study center.

multivariable analyses including the covariates age, sex, FEV_1, BMI z-score, *Pseudomonas aeruginosa* infection, and *CFTR* genotype [7]. As expected, all pre-defined covariates were significant predictors of VO_{2peak}, strengthening our approach. It is challenging to directly compare our multivariable models to those of previous investigators studying the role of glucose intolerance/CFRD on VO_{2peak} due to inclusion of different study populations (i.e., adults versus children), outcome selection (i.e., VO_{2peak} expressed in mL.kg^{-1}.min^{-1} or mL.min^{-1}), and confounder control [8,13]. The fact that we did not observe differences in clinical characteristics, nutritional status, lung function and aerobic exercise capacity between individuals with and without CFRD might be due to a selection bias. Evidence from large studies suggest that CFRD is associated with worse lung function, nutritional status and reduced life expectancy [3,4,31]. We cannot exclude that the subgroup with CFRD represents a selection of active and health conscious people with CF who may receive more intense education and support from their CF care team because of their diabetic status, which could explain the lack of between-group difference in respect to disease status including physical activity levels, and VO_{2peak}. On the other hand, one would assume that self-selection bias into a study occurs at a study population level, irrespective of presence or absence of CFRD. Although, the beneficial effects of the anabolic hormone insulin are not universally agreed in the literature [1,37] one cannot rule out a possible impact of insulin on muscle protein synthesis and thus exercise capacity in CF. Nevertheless, the multivariable models including adjustment for potential confounders showed no differences in VO_{2peak} between groups with and without CFRD. This was also true for models comparing participants with normal glucose tolerance to those with impaired glucose tolerance and CFRD.

A major strength of our study is the inclusion of physical activity as an important predictor of VO_{2peak} in our multivariable models [10,33], a limitation of previous studies [8,13]. It is reasonable to speculate that (unadjusted) differences in VO_{2peak} between groups of individuals with and without CFRD or normal glucose tolerance versus impaired glucose tolerance/CFRD are (partly) due to differences in habitual physical activity levels [8,13,14] and other important covariates such as lung disease severity and nutritional status. In our study, self-reported vigorous physical activity and objectively measured step count were not different between participants with and without CFRD enhancing group comparability in terms of this important covariate. Nevertheless, physical activity – along with other potential confounders – was a significant predictor of VO_{2peak} in our models, consistent with previous research [10,33]. We acknowledge that a 7-day step count measurement may not capture the full spectrum of a person's physical activity because pedometry cannot measure activities such as swimming, cycling or resistance training. We treated physical activity as a potential confounder in our models due to the well-known beneficial effect of an active lifestyle on glucose metabolism, and its protective role on the development of non-insulin dependent diabetes [38,39]. Whether a physically active lifestyle can prevent or delay the onset of CFRD in CF lung disease is unknown. On the other hand, physical inactivity maybe a consequence of the presence of CFRD and could be perceived as a barrier because of the additional burden of blood glucose control when doing structured physical activity [1]. In this case, physical activity would per se not fulfill the criterion of a confounder and therefore not qualify to be a covariate in our models (i.e., physical activity would act as mediator between CFRD and VO_{2peak}). Conceptually, identifying potential confounders in a cross-sectional study design is challenging and it is difficult to properly distinguish between a potential confounder and mediator due to a lack of information on the temporal order of the covariates of interest. Consequently, adjustment for a mediator on the causal relationship between an exposure and outcome may introduce bias [40]. For these reasons, we run a simplified model with VO_{2peak} as dependent variable including the covariates age, sex and CFRD (**Table S4**). In this model, CFRD was also not a significant predictor of VO_{2peak}, consistent with the unadjusted analysis, the basic model including age, sex, weight, FEV_1 and CFRD (**Table S5**), and the fully adjusted multivariable models (Table 4). All analyses revealed no associations between CFRD and VO_{2peak}.

Notably, limited data are available on the effects of regular physical activity on blood glucose control in people with CF lung disease. ACTIVATE-CF, the largest intervention study to date, did not show beneficial effects on blood glucose between the physical activity intervention and control groups after 9-months [19]. Further research is warranted to study the role of regular physical activity on the development of CFRD in the modern era of CF care.

4.1. Limitations

This study has several limitations. The study population is composed of children and adults that took part in an international multicenter physical activity trial conducted across eight countries and 27 CF centers [19]. All data were collected prospectively according to study-specific standard operating procedures to ensure high-quality standards, but we cannot rule out between-center variability in respect to quality of treatment, and physical activity prescription. Participation bias may have occurred limiting the generalizability of our findings to the overall population of people living with CF including those that are less interested in physical activity. Moreover, this study was conducted before widespread availability of highly effective triple combination modulator therapies [41,42]; the impact of those therapies on blood glucose control [43], physical activity, aerobic exercise capacity and muscle function remains to be studied in detail. Our study sample is the largest to investigate associations between CFRD and VO_{2peak}, however, the number of people with CFRD in this study was small (n = 19). Moreover, there is a clear association between severity of *CFTR* genotype and the development of CFRD in CF lung disease [4,31], the role of *CFTR* genotype on VO_{2peak} remains controversial [7,34]. The largest study to date revealed no association between

CFTR genotype class and VO_{2peak} in an international cohort of 726 children and adults with CF [7], but the current study is clearly not powered to evaluate the role of *CFTR* genotype as a prognostic factor in the relationship between CFRD and VO_{2peak}. Notably, our analysis is limited to maximal CPET variables; it remains to be investigated if submaximal CPET variables (e.g., gas exchange threshold, ventilatory inefficiency) yield differences between individuals with and without CFRD. In the ACTIVATE-CF trial, we did not perform an OGTT at study entry in participants with an established diagnosis of CFRD nor did we collect their glycated hemoglobin (HbA1c) levels throughout the trial [1]. This information would have provided further insights into the severity of CFRD. A single hypoglycemic event was reported as an adverse event in an intervention group participant at night following 3 h of intense exercise and inadequate food intake. This apart, no participant became hypoglycemic as a result of CPET or physical activity, suggesting stable blood sugar control for the CFRD group as a whole. Finally, we were not able to include all potential confounders (e.g., pulmonary exacerbations in the previous year) in our models to study associations between CFRD and VO_{2peak}, thus, residual confounding might still be present.

5. Conclusions

This international multicenter study suggests no meaningful differences in VO_{2peak} between people with and without CFRD given comparable levels of physical activity.

Author declaration form

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. We confirm that the manuscript entitled *"Cystic fibrosis related diabetes is not associated with maximal aerobic exercise capacity in cystic fibrosis: a cross-sectional analysis of an international multicenter trial (ACTIVATE-CF)"* has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author and which has been configured to accept email from (thomas.radtke@uzh.ch).

Thomas Radtke (corresponding author) on behalf of all authors (15.04.2022).

Funding

ACTIVATE-CF is an investigator-initiated trial. The study was supported by Mukoviszidose e.V.; Cystic Fibrosis Switzerland (CFS); Cystic Fibrosis Canada; Vaincre la Mucoviscidose (France); Nederlandse Cystic Fibrosis Stichting; Edinburgh Children's Hospital Charity; The Swiss National Science Foundation; the Cystic Fibrosis Foundation; and Mylan Healthcare GmbH. The international coordination of the project was funded through a Vertex Innovation Award which is an unconditional research grant provided by Vertex Pharmaceuticals (Europe) Limited. The funding bodies had no role in the design of the study, data collection, and in the writing of this manuscript.

Conflict of interest

None.

CRediT authorship contribution statement

Thomas Radtke: Conceptualization, Data curation, Investigation, Methodology, Visualization, Project administration, Supervision, Writing – original draft. **Susi Kriemler:** Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Writing – review & editing. **Lothar Stein:** Data curation, Investigation, Project administration, Resources, Writing – review & editing. **Chantal Karila:** Funding acquisition, Data curation, Investigation, Resources, Writing – review & editing. **Don S Urquhart:** Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Supervision, Writing – review & editing. **David M Orenstein:** Conceptualization, Data curation, Funding acquisition, Resources, Writing – review & editing. **Larry C Lands:** Conceptualization, Data curation, Funding acquisition, Methodology, Resources, Supervision, Writing – review & editing. **Christian Schindler:** Conceptualization, Formal analysis, Methodology, Supervision, Writing – review & editing. **Ernst Eber:** Funding acquisition, Data curation, Investigation, Methodology, Resources, Supervision, Writing – review & editing. **Sarah R Haile:** Data curation, Formal analysis, Methodology, Supervision, Writing – review & editing. **Helge Hebestreit:** Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2022.06.012.

References

[1] Moran A, Brunzell C, Cohen RC, Katz M, Marshall BC, Onady G, et al. Clinical care guidelines for cystic fibrosis-related diabetes: a position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. Diabetes Care 2010;33:2697–708. doi:10.2337/dc10-1768.

[2] Moran A, Dunitz J, Nathan B, Saeed A, Holme B, Thomas W. Cystic fibrosis-related diabetes: current trends in prevalence, incidence, and mortality. Diabetes Care 2009;32:1626–31. doi:10.2337/dc09-0586.

[3] Kerem E, Viviani L, Zolin A, MacNeill S, Hatziagorou E, Ellemunter H, et al. Factors associated with FEV1 decline in cystic fibrosis: analysis of the ECFS patient registry. Eur Respir J 2014;43:125–33. doi:10.1183/09031936.00166412.

[4] Lewis C, Blackman SM, Nelson A, Oberdorfer E, Wells D, Dunitz J, et al. Diabetes-related mortality in adults with cystic fibrosis. role of genotype and sex. Am J Respir Crit Care Med 2015;191:194. doi:10.1164/rccm.201403-0576OC.

[5] White H, Pollard K, Etherington C, Clifton I, Morton AM, Owen D, et al. Nutritional decline in cystic fibrosis related diabetes: the effect of intensive nutritional intervention. J Cyst Fibros 2009;8:179–85. doi:10.1016/j.jcf.2008.12.002.

[6] Bridges N, Rowe R, Holt RIG. Unique challenges of cystic fibrosis-related diabetes. Diabet Med 2018 Online ahead of print. doi:10.1111/dme.13652.

[7] Radtke T, Hebestreit H, Gallati S, Schneiderman JE, Braun J, Stevens D, et al. CFTR GENOtype and maximal exercise capacity in cystic fibrosis a cross-sectional study. Ann Am Thorac Soc 2018;15:209–16. doi:10.1513/AnnalsATS.201707-570OC.

[8] Causer AJ, Shute JK, Cummings MH, Shepherd AI, Wallbanks SR, Allenby MI, et al. The implications of dysglycaemia on aerobic exercise and ventilatory

function in cystic fibrosis. J Cyst Fibros 2020;19:427–33. doi:10.1016/j.jcf.2019.09.014.
[9] Pastre J, Prevotat A, Tardif C, Langlois C, Duhamel A, Wallaert B. Determinants of exercise capacity in cystic fibrosis patients with mild-to-moderate lung disease. BMC Pulm Med 2014;14:74. doi:10.1186/1471-2466-14-74.
[10] Hebestreit H, Kieser S, Rudiger S, Schenk T, Junge S, Hebestreit A, et al. Physical activity is independently related to aerobic capacity in cystic fibrosis. Eur Respir J 2006;28:734–9.
[11] Lands LC, Heigenhauser GJF, Jones NL. Analysis of factors limiting maximal exercise performance in cystic fibrosis. Clin Sci 1992;83:391–7.
[12] Junge S, Kueck M, Tegtbur U, Thon A, Stein L, Bartels J. Exercise capacity of adolescents with cystic fibrosis related diabetes. Ped Pulmonol 2013:360 Conference abstract.
[13] Foster K, Huang G, Zhang N, Crisalli J, Chini B, Amin R, et al. Relationship between exercise capacity and glucose tolerance in cystic fibrosis. Pediatr Pulmonol 2018;53:154–61. doi:10.1002/ppul.23906.
[14] Tomlinson OW, Stoate ALE, Dobson L, Williams CA. The effect of dysglycaemia on changes in pulmonary and aerobic function in cystic fibrosis. Front Physiol 2022;13.
[15] Burghard M, Takken T, Nap-van der Vlist MM, Nijhof SL, van der Ent CK, Heijerman HGM, et al. Physiological predictors of cardiorespiratory fitness in children and adolescents with cystic fibrosis without ventilatory limitation. Ther Adv Respir Dis 2022;16:17534666211070144. doi:10.1177/17534666211070143.
[16] Hebestreit H, Hulzebos EHJ, Schneiderman JE, Karila C, Boas SR, Kriemler S, et al. Cardiopulmonary exercise testing provides additional prognostic information in cystic fibrosis. Am J Respir Crit Care Med 2019;199:987–95. doi:10.1164/rccm.201806-1110OC.
[17] van de Weert-van Leeuwen PB, Slieker MG, Hulzebos HJ, Kruitwagen CL, van der Ent CK. Arets HG. Chronic infection and inflammation affect exercise capacity in cystic fibrosis. Eur Respir J 2012;39:893–8. doi:10.1183/09031936.00086211.
[18] Cox N, Holland A, Alison J, Dwyer T. Physical activity in cystic fibrosis related diabetes. Eur Respir J 2018;52:PA5429.
[19] Hebestreit H, Kriemler S, Schindler C, Stein L, Karila C, Urquhart DS, et al. Effects of a partially supervised conditioning program in cystic fibrosis: an international multicenter randomized controlled trial (ACTIVATE-CF). Am J Respir Crit Care Med 2022;205:330–9. doi:10.1164/rccm.202106-1419OC.
[20] Hebestreit H, Lands LC, Alarie N, Schaeff J, Karila C, Orenstein DM, et al. Effects of a partially supervised conditioning programme in cystic fibrosis: an international multi-centre randomised controlled trial (ACTIVATE-CF): study protocol. BMC Pulm Med 2018;18:31. doi:10.1186/s12890-018-0596-6.
[21] Godfrey S, Mearns M. Pulmonary function and response to exercise in cystic fibrosis. Arch Dis Child 1971;46:144–51.
[22] Orenstein DM. Assessment of exercise pulmonary function. In: Rowland TW, editor. Pediatric laboratory exercise testing clinical guidelines. Champaign: Human Kinetics; 1993. p. 141–63.
[23] Radtke T, Crook S, Kaltsakas G, Louvaris Z, Berton D, Urquhart DS, et al. ERS Statement on Standardisation of Cardiopulmonary Exercise Testing in Chronic Lung Diseases. Eur Respir Rev 2019;28:180101.
[24] Godfrey S, Davies CT, Wozniak E, Barnes CA. Cardio-respiratory response to exercise in normal children. Clin Sci 1971;40:419–31.
[25] Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J 2005;26:319–38. doi:10.1183/09031936.05.00034805.
[26] Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, et al. Standardisation of the measurement of lung volumes. Eur Respir J 2005;26:511–22. doi:10.1183/09031936.05.00035005.
[27] Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J 2012;40:1324–43. doi:10.1183/09031936.00080312.
[28] Lederer DJ, Bell SC, Branson RD, Chalmers JD, Marshall R, Maslove DM, et al. Control of confounding and reporting of results in causal inference studies. Guidance for authors from editors of respiratory, sleep, and critical care journals. Annals ATS 2019;16:22–8. doi:10.1513/AnnalsATS.201808-564PS.
[29] Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology 1999;10:37–48.
[30] Tennant PWG, Murray EJ, Arnold KF, Berrie L, Fox MP, Gadd SC, et al. Use of directed acyclic graphs (DAGs) to identify confounders in applied health research: review and recommendations. Int J Epidemiol 2021;50:620–32. doi:10.1093/ije/dyaa213.
[31] Olesen HV, Drevinek P, Gulmans VA, Hatziagorou E, Jung A, Mei-Zahav M, et al. Cystic fibrosis related diabetes in Europe: prevalence, risk factors and outcome; Olesen et al. J Cyst Fibros 2020;19:321–7. doi:10.1016/j.jcf.2019.10.009.
[32] Lin Y-C, Keenan K, Gong J, Panjwani N, Avolio J, Lin F, et al. Cystic fibrosis–related diabetes onset can be predicted using biomarkers measured at birth. Genet Med 2021;23:927–33. doi:10.1038/s41436-020-01073-x.
[33] Savi D, Di Paolo M, Simmonds N, Onorati P, Internullo M, Quattrucci S, et al. Relationship between daily physical activity and aerobic fitness in adults with cystic fibrosis. BMC Pulm Med 2015;15:59. doi:10.1186/s12890-015-0036-9.
[34] Selvadurai HC, McKay KO, Blimkie CJ, Cooper PJ, Mellis CM, Van Asperen PP. The relationship between genotype and exercise tolerance in children with cystic fibrosis. Am J Respir Crit Care Med 2002;165:762–5.
[35] Kerem E, Corey M, Kerem BS, Rommens J, Markiewicz D, Levison H, et al. The relation between genotype and phenotype in cystic fibrosis–analysis of the most common mutation (delta F508). N Engl J Med 1990;323:1517–22. doi:10.1056/NEJM199011293232203.
[36] Nevill AM. The appropriate use of scaling techniques in exercise physiology. Pediatr Exerc Sci 1997;9:295–8.
[37] Warren RE. Cystic fibrosis and insulin therapy: a reality check. Diabetic Medicine 2019;36:1360–4. doi:10.1111/dme.13959.
[38] Colberg SR, Sigal RJ, Fernhall B, Regensteiner JG, Blissmer BJ, Rubin RR, et al. Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement. Diabetes Care 2010;33:e147–67. doi:10.2337/dc10-9990.
[39] LaMonte MJ, Blair SN, Church TS. Physical activity and diabetes prevention. J Appl Physiol 2005;99:1205–13. doi:10.1152/japplphysiol.00193.2005.
[40] Groenwold RHH, Palmer TM, Tilling K. To adjust or not to adjust? When a "confounder" is only measured after exposure. Epidemiology 2021;32:194–201. doi:10.1097/EDE.0000000000001312.
[41] Middleton PG, Mall MA, Dřevínek P, Lands LC, McKone EF, Polineni D, et al. Elexacaftor-tezacaftor-ivacaftor for cystic fibrosis with a single Phe508del Allele. N Engl J Med 2019;381:1809–19. doi:10.1056/NEJMoa1908639.
[42] Heijerman HGM, McKone EF, Downey DG, Van Braeckel E, Rowe SM, Tullis E, et al. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. Lancet 2019;394:1940–8. doi:10.1016/S0140-6736(19)32597-8.
[43] Scully KJ, Marchetti P, Sawicki GS, Uluer A, Cernadas M, Cagnina RE, et al. The effect of elexacaftor/tezacaftor/ivacaftor (ETI) on glycemia in adults with cystic fibrosis. J Cyst Fibros 2022;21(2):258–63. doi:10.1016/j.jcf.2021.09.001.