Original Article

# Trajectories of early growth and subsequent lung function in cystic fibrosis: An observational study using UK and Canadian registry data

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## ARTICLE INFO

## ABSTRACT

*Background:* Understanding the pulmonary impact of changes in early life nutritional status over time in a paediatric CF population may help inform how to use nutritional assessment to guide clinical care. National registry data provides an opportunity to study patterns of weight gain over time at the level of the individual, and thus to gain detailed understanding of the relationship between early weight trajectories and later lung function in children with Cystic Fibrosis (CF).

*Methods:* Using data from the United Kingdom (UK) and Canadian CF Registries, a mixed effects linear regression model was used to describe children's weight and BMI z-score trajectories from age 1 to 5 years. The intercept (weight-for-age at age 1) and slope (weight-for-age trajectory) from this model were then used as covariates in a linear regression of first lung function measurement at age 6 years.

*Results:* In both the UK and Canadian data, greater weight-for-age z-score at age 1 year and greater change in weight-for-age over time were associated with higher $FEV_1$% predicted. A greater weight-for-age z-score at age 1 year was associated with a higher $FEV_1$% predicted (UK: 3.78% (95% CI: 1.76; 4.70); Canada: 3.20% (95%CI: 1.76; 4.70)). These associations were reproduced for BMI z-scores and FVC% predicted.

*Conclusions:* Early weight-for-age, specifically at age 1 year, and weight-for-age trajectories across early childhood are associated with later lung function. This relationship persists after adjustment for potential confounders. Current guidelines may need to be updated to place less emphasis on a specific cut-off (such as the 10th percentile) and encourage tracking of weight-for-age over time.

## 1. Introduction

Cystic fibrosis (CF) is an inherited multi-system disease. One of the clinical manifestations is the lack of pancreatic enzymes in the digestive system which leads to malabsorption of nutrients, and thus increases the risk of malnutrition and poor prognosis. Therefore, optimizing nutrition and nutrient absorption is a critical aspect of CF care. Low weight has been found to be associated with key health outcomes in CF, such as: poor lung function [1–3]; increased risk of pulmonary exacerbations [4]; higher likelihood of

lung transplantation [5]; as well as increased risk of death [6]. Thus, maintaining a typical weight-for-age percentile and rate of weight gain is considered to be a vital component in maintaining overall health in children with CF. Measurements of weight (and height) are used clinically to track nutritional status, and are especially important in early childhood when other measures of disease progression such, as lung function, are not readily available.

In general, international clinical care guidelines for children with CF recommend careful observation or nutritional intervention (such as oral supplementation) when body mass index (BMI)-for-age is below the 10th percentile of a healthy population [7]. Maintaining BMI above the 50th percentile is widely recommended [7–9]. Although there are variations to this guidance between coun-

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tries, low BMI values often warrant enhanced follow-up or intervention. The recommended cut offs (such as 10th centile [1]) are derived from studies which found an association between weight-for-age (or BMI-for-age) and poor lung function in later childhood. Cut-offs are convenient and readily interpretable; however, dividing a measure such as weight-for-age which is a continuous scale into discrete categories relative to a healthy population does not capture the heterogeneity of individual growth trajectories within these categories, and potentially obscures non-linear associations between weight-for-age and lung function [10].

Understanding the pulmonary impact of changes in early life nutritional status (weight-for-age and BMI-for-age) over time in a paediatric CF population may help inform how to use nutritional assessment to guide clinical care. In this study we aim to characterise the association between weight-for-age trajectories in early childhood (1 to 5 years) and lung function at age 6 years using two national CF populations.

## 2. Methods

### 2.1. Data

Data from two national CF registries (United Kingdom (UK) and Canada) were used. The UK Cystic Fibrosis Trust database committee approved the use of pseudo-anonymized data in this study. This study was approved by the Research Ethics board of the Hospital for Sick Children, Toronto, Canada (REB#1,000,051,441). Both the UK and Canada have universal health care coverage such that there are no financial barriers to receiving specialist CF care. CF charities in both countries provide financial incentives to submit data to the registries and thus the registries capture nearly all people with CF (pwCF). Further data completion is high, especially for core variables such as demographics and annual weight and lung function measurements [11,12]. Both registries undergo routine data checks for implausible and missing values. Annual stable clinical measures are obtained from care encounters when pwCF are not experiencing periods of ill health such as exacerbations. Though the Canadian Registry includes encounter-based records since 2012, annual review data from clinically stable visits were used in order to be consistent with the UK data.

The study population included all pwCF in the registries born between 2000 and 2011 with at least one measurement of weight between 1 and 5.5 years and the first lung function measure (forced expiratory volume in one second, $FEV_1$ and forced vital capacity, FVC) recorded at closest to 6 years (from 5.5 to 7.5 years). Weight, measured in kilograms, was converted to weight-for-age z-scores using the British 1990 growth reference to create a continuous, standardized measure of weight-for-age across early childhood [13] (weight-for-age will refer to weight-for-age z-scores throughout this study). Absolute measures of lung function ($FEV_1$ and FVC) were converted to z-scores and percent predicted using the Global Lung Function Initiative (GLI) reference equations [14]. Both z-scores and percent predicted were included in descriptive tables, but percent predicted was used in statistical models for ease of interpretation and given the narrow age range over which lung function was measured.

### 2.2. Statistical analysis

A mixed effects linear regression model was used to describe weight z-score trajectories from age 1 to 5. A random intercept and slope for each individual was included. We tested for the inclusion of a natural cubic spline for age to account for non-linear average trajectory. In all models a cubic spline with three knots was required, apart from the Canadian BMI model, in which two knots

were selected. Age was centred at one year for ease of interpretation. Each individual's trajectory was summarized as their weight z-score at age one year (intercept) and change in weight-for-age over time (slope). Since the age variable was fitted with a spline, the slope term refers to the linear component of change over time.

We then investigated the association between intercept and slope of the weight-for-age trajectories and $FEV_1$% and FVC% measurements from the first lung function test. This was done using separate linear regression models for $FEV_1$% and FVC%. As the slope and intercept for each individual's weight-for-age were estimated from a regression rather than measured directly, non-parametric bootstrapping was used to account for the extra uncertainty [15]. Significance at the 5% level is inferred if the 95% confidence interval does not cross zero. A complete case analysis was carried out.

The first models were fitted with three covariates only: weight-for-age intercept, weight-for-age slope and age at lung function test. The next models were fitted with a range of baseline covariates in order to control for potential confounding: sex; birth year; area -level index of multiple deprivation (IMD) z-score (UK dataset only); pancreatic insufficiency (PI); F508del genotype group (homozygous; heterozygous; other); age at diagnosis and clinical status at diagnosis (levels: asymptomatic newborn screened; meconium ileus (MI); symptoms; other). The levels for the clinical status at diagnosis were derived using information from the time of diagnosis, including whether the infant had been newborn screened or not, and whether there were any significant symptoms present at the time. Any infants who were newborn screened with no symptoms were assigned 'asymptomatic NBS'. Infants who had symptoms present, including respiratory problems, were assigned 'symptomatic', whether they were newborn screened or not. The additional 'age at diagnosis' variable accounted for the likely difference in age at diagnosis between the those who were symptomatic and diagnosed by newborn screening compared to those who were not. Meconium ileus was treated as a separate category from other symptoms.

Analyses were conducted separately in the UK and Canadian datasets. Weight-for-age was the primary measure of nutritional status with additional analysis using body mass index (BMI). An additional analysis was carried out re-fitting the simple model for $FEV_1$% on weight-for-age intercept, slope and age at lung function test; with the intercept and slopes derived using the commonly used combined World Health Organisation and British 1990 Ref. [16]. The analyses were carried out using R statistical software with the packages 'lme4'and 'boot' [17–19].

## 3. Results

Fig. 1 describes the inclusion and exclusion of participants for each Registry. A total of 1974 pwCF were included in the analysis from the UK Registry, 791 from the Canadian registry. Those who were excluded for having missing data in the UK Registry were born on average earlier than the complete cases cohort: median year of birth 2003 and 2006 respectively. A consequence of this is that more of the complete case cohort were diagnosed asymptomatically by NBS (48% compared to 34% in those with missing data). There were minimal other differences between those with missing data and the complete case in the UK data. The only difference between complete cases and participants with missing data detected in the Canadian data was a slightly earlier year of birth (median year of birth 2004 in the complete cases; 2006 in those missing some data). All other characteristics were similar.

The characteristics of the study population included in the UK and Canadian datasets were similar with the exception of presentation at diagnosis (Table 1). Almost half of the UK group were asymptomatic at diagnosis (48.1%) compared to 25.0% of the
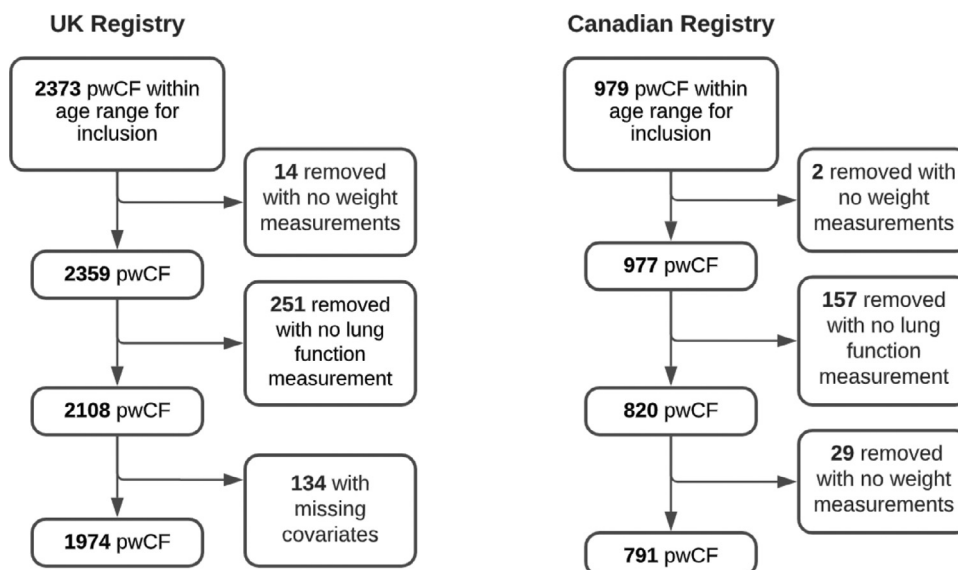
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**UK Registry**

**2373** pwCF within age range for inclusion

→ **14** removed with no weight measurements

**2359** pwCF

→ **251** removed with no lung function measurement

**2108** pwCF

→ **134** with missing covariates

**1974** pwCF

**Canadian Registry**

**979** pwCF within age range for inclusion

→ **2** removed with no weight measurements

**977** pwCF

→ **157** removed with no lung function measurement

**820** pwCF

→ **29** removed with no weight measurements

**791** pwCF

**Fig. 1.** Flow diagram of inclusion and exclusion of participants.

**Table 1**

Summary UK and Canadian Registry data 2000 – 2016 with at least one weight measurement and one lung function measurement at age 6 years (5.5–7.5 years).

|  | UK Registry $n = 1974$ | Canadian Registry $n = 791$ |
|---|---|---|
| Weight z-score at first measurement (mean (SD)) | −0.6 (1.3) | −1.4 (1.5) |
| BMI z-score at first measurement (mean (SD)) | −0.2 (1.2) | −1.0 (1.6) |
| FEV$_1$% at first measurement (mean (SD)) | 89.2 (16.1) | 95.5 (18.6) |
| FEV$_1$ z-score at first measurement (mean (SD)) | −0.8 (1.3) | −0.3 (1.5) |
| Sex (Female) (%) | 979 (49.6%) | 387 (48.9%) |
| Year of birth (median [IQR]) | 2006 [2004, 2008] | 2004 [2002, 2008] |
| Pancreatic insufficient = Y (%) | 1717 (87.0%) | 714 (90.3%) |
| F508 genotype (%) |  |  |
| Homozygous | 1079 (54.7%) | 396 (50.1%) |
| Heterozygous | 716 (36.3%) | 310 (39.2%) |
| Other | 179 (9.1%) | 85 (10.7%) |
| Presentation at Diagnosis (%) |  |  |
| Asymptomatic | 949 (48.1%) | 198 (25.0%) |
| Meconium Ileus | 395 (20.0%) | 127 (16.1%) |
| Symptoms | 566 (28.7%) | 404 (51.1%) |
| Other | 64 (3.2%) | 62 (7.8%) |
| Age at diagnosis, years (median [IQR]) | 0.1 [0.1, 0.3] | 0.3 [0.1, 1.6] |
| No. weight measurements (median [IQR]) | 5.0 [3.0, 5.0] | 5.0 [4.0, 6.0] |
| IMD z-score (UK only) | −0.3 [−0.8, 0.5] | – |
| Number of *Pseudomonas* infections (median [IQR]) | 1 [0, 2] | 1 [0, 2] |
| Number of *Staph* infections (median [IQR]) | 0 [0, 1] | 4 [1, 8] |
| Number of *Hflu* infections (median [IQR]) | 0 [0, 1] | 1 [0, 3] |

Canadian group. The proportion of pwCF diagnosed by newborn screening was also higher in the UK.

The average fitted weight-for-age and BMI trajectories from age 1 to 5 years are shown in Fig. 2 and highlight that weight-for-age changes are not linear in the first 5 years of life. There is a small increase to approximately age 2.5 years, after which weight-for-age and BMI z-scores plateau and are close to zero. Change over time was modest: 85% of pwCF in the UK data changed by less than 0.2 wt-for-age z-scores per year; 80% in the Canadian data. Of note there was a high degree of variation around this average weight-for-age z-score (and BMI) at age 1 year, with z-scores ranging from −4 to 2.5.

In both the UK and Canadian data, there was evidence that weight-for-age at age 1 year (intercept) and change over time (slope) were associated with FEV$_1$% later in childhood (Table 2). In the simple model adjusted only for age at first lung function test, children with greater weight-for-age at age 1 year had higher lung function later in childhood: an increase in one weight-for-age z-score was associated with an increase of 3.78 (3.04, 4.53) FEV$_1$% in the UK data and 3.20 (95% CI: 1.78, 4.70) in the Canadian data. An increase in one z-score for weight-for-age at age 1 year from −1 to 0 is equivalent to an increase of approximately 35 centiles. The magnitude of the different in centiles varies across the scale of the z-scores. For more examples in terms of centiles and kilograms see Supplementary Table 4 and supplementary Fig. 1. Similarly, there was evidence that children whose weight-for-age z-score increased over time (and so had a positive slope) had better lung function at age 6. A child with a slope of 0.07 z-scores per year (the 75th percentile for weight-for-age z-score slopes in the UK) would be expected to have a higher predicted first FEV$_1$% of 2.72 compared with a child with a slope of −0.08 (the 25th percentile) (Fig. 3). These plots display the differences in lung function between pwCF with low and high weight-for-age at age 1 year, as well as the high degree of unexplained variation in FEV1% at age 6.

The association between weight-for-age z-score at age 1 year and FVC% was similar in magnitude to FEV$_1$% (Table 2). An increase

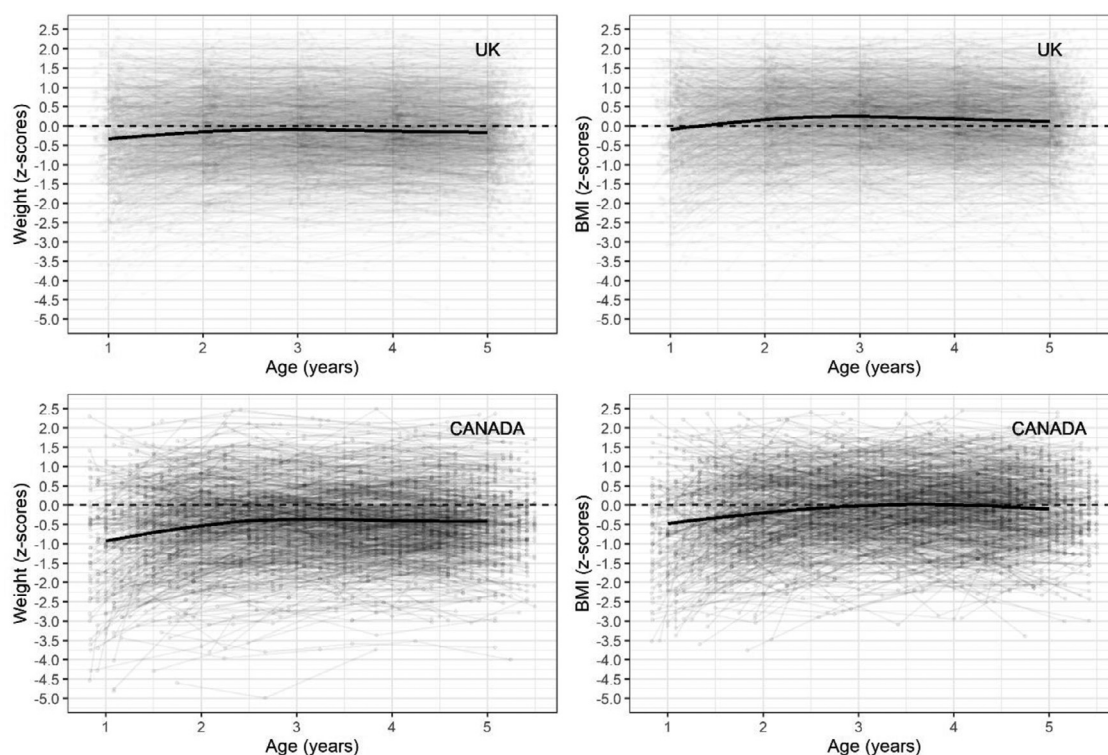A. Macdougall, D. Jarvis, R.H. Keogh et al.

**Fig. 2.** Weight-for-age and BMI for the UK (top row) and Canada (bottom row). Raw data is shown in grey, fitted average trajectories shown in black.

**Table 2**

Estimated coefficients from unadjusted and adjusted linear regressions of lung function (FEV$_1$% left, or FVC% right) on weight-for-age or BMI z-score age 1 year and slope age 1 to 5 years, in the UK and Canadian CF registry data. [1]Simple models included age at lung function test as the only covariate alongside weight-for-age slope and intercept; [2]Fully adjusted models additionally included the following covariates: sex; year of birth; IMD z-score (UK only); delta F508 class genotype class; presentation at diagnosis; age at diagnosis. All coefficients shown in supplementary Table 1.

| Weight-for-age z-scores | FEV$_1$% | | FVC% | |
|---|---|---|---|---|
| | UKn=1974 | Canadan=791 | UKn=1974 | Canadan=791 |
| Model 1: Simple[1] | | | | |
| Weight z-score age 1 (z-scores) | 3.78 [3.04, 4.53] | 3.20 [1.76, 4.70] | 3.71 [2.33, 5.15] | 3.79 [2.33, 5.15] |
| Weight z-score slope (0.1 z-scores) | 1.70 [1.23, 2.15] | 1.19 [0.26, 2.16] | 1.51 [0.04, 1.79] | 0.94 [0.01, 1.81] |
| Model 2: Fully adjusted[2] | | | | |
| Weight z-score age 1 (z-scores) | 3.40 [2.63, 4.19] | 3.03 [1.52, 4.56] | 3.41 [2.63, 4.21] | 3.80 [2.29, 5.23] |
| Weight z-score slope (0.1 z-scores) | 1.61 [1.13, 2.07] | 0.96 [0.01, 1.92] | 1.46 [0.98, 1.95] | 0.84 [−0.02, 1.75] |
| BMI z-scores | | | | |
| Model 1: Simple[1] | | | | |
| BMI z-score age 1 (z-scores) | 4.13 [3.26, 5.01] | 3.70 [2.02, 5.41] | 4.30 [3.26, 5.01] | 3.44 [1.65, 5.21] |
| BMI z-score slope (0.1 z-scores) | 1.96 [1.43, 2.50] | 1.10 [0.21, 2.06] | 1.91 [1.43, 2.50] | 0.68 [−0.34, 1.66] |
| Model 2: Fully adjusted[2] | | | | |
| BMI z-score age 1 (z-scores) | 3.90 [3.04, 4.77] | 3.52 [1.77, 5.23] | 4.12 [3.29, 5.01] | 3.48 [1.68, 5.20] |
| BMI z-score slope (0.1 z-scores) | 1.86 [1.31, 2.42] | 1.10 [0.14, 2.06] | 1.83 [1.35, 2.36] | 0.81 [−0.19, 1.77] |

of approximately 4.0 FVC% was found for each increase in z-score of weight-for-age at age 1 year. There was a smaller association between weight-for-age increase over time (i.e. slope) and FVC% in both datasets (Table 2).

The estimated associations using BMI z-score intercept and slope with first FEV$_1$% and FVC% (Table 2) were greater in magnitude compared to the analysis using weight-for-age z-scores. An increase of one BMI z-score at age 1 year was associated with an increase of 4.13 FEV$_1$% (95% CI: 3.26, 5.01) in the UK data, and 3.70 FEV$_1$% (95% CI: 2.02, 5.41) in the Canadian data. Increasing BMI z-score over time was found to be associated with greater FEV$_1$% only in the UK (UK: 1.96, CI: 1.43, 2.50; Canada: 0.68, CI: −0.34, 1.66).

Adjustment for confounders attenuated the association, but in most cases, there was still strong evidence of an association

(Table 2). Supplementary Tables 1 and 2 contain estimates for all confounders included in the weight-for-age z-score and BMI z-score models respectively. Supplementary Table 3 contains the results for the simple model re-run using the UK-WHO growth reference. The results were very similar to the original analysis.

## 4. Discussion

Weight-for-age z-score at age 1 year and weight-for-age z-score change during early childhood were both associated with first lung function measure in childhood, as measured by FEV$_1$% and FVC% at the age of 6 years. Although we cannot comment on the causal relationship, our individualized trajectory approach suggests that, amongst pwCF with similar nutrition at age 1, there is a risk of lower lung function at age 6 years if their weight-for-age is not
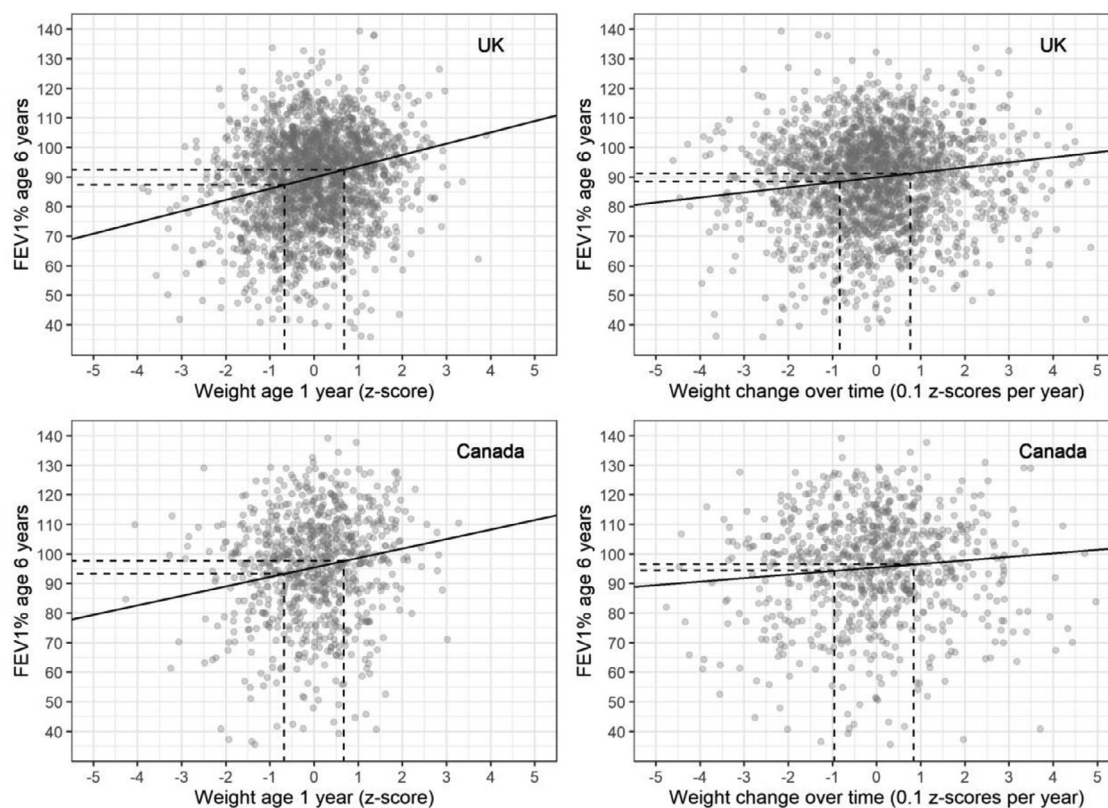
**Fig. 3.** Scatter plots of FEV1% against weight-for- age 1 year (left) and weight-for-age slope (right) in the UK and Canada (bottom). Solid line indicates the fitted regression lines. Dashed lines indicate predicted lung function for the 25th and 75th centile for predicted weight-for-age at age 1 or change over time.

maintained. These results were consistent across two large paediatric populations of children with CF, when using weight-for-age or BMI as the nutritional marker, and when potential confounders were adjusted for.

The greatest difference in lung function was between those with a lower and higher weight-for- age 1 year. In both the UK and Canadian data, it was not possible to make up for this gap with increasing weight-for-age from age 1 to 5 years. Most pwCF did not change weight-for-age or BMI z-score by more than a small amount after the first 2 years of life. This further highlights that genetic and prenatal factors, as well as exposure within the first year of life may be important contributors to disease progression. Inclusion of birth weight and weight measurements in the registry during the first year of life may help to identify specific thresholds for nutritional status following a CF diagnosis.

The existing literature in this field has mostly reported differences in $FEV_1$% at age 6 years between the groups with highest and lowest categories of weight in early life. Our results are consistent with the literature but also highlight that children of all weights who experience a decline in their nutritional status may be at risk of poor lung function later in childhood. It is not possible to define a specific threshold of decline that would warrant clinical intervention from these data, nonetheless precipitous weight loss either acutely during a pulmonary exacerbation or gradually over time does warrant careful monitoring and follow-up irrespective of whether weight is in the normal range. Further work is needed to identify clinically relevant thresholds that are anchored to patient-centred outcomes.

We cannot directly compare results to previous literature as there is heterogeneity in how nutritional status was defined. Konstan et al. categorised pwCF according to whether they remained below, above or crossed the 10th centile for weight between age 3 and 6 years. A group difference of approximately 16 $FEV_1$% was

found between those who stayed above the 10th percentile of weight-for-age between age 3–6 years compared to those who stayed below [1]. Sanders et al.'s study of children from the US CF Registry defined groups of pwCF according to change in weight for length and BMI percentiles (always over 50th centile; increased by over 10%; stable or decreased by over 10%). They reported a difference of 5.4 $FEV_1$% points between those whose weight-for-length or BMI percentile increased by more than 10 centiles and those whose weight decreased by more than 10 centiles [20]. Woestenenk et al. reported differences according to weight z-score at 2 years (over 0, from −1 to 0, below −1) in a Dutch cohort [3]. Differences were found of approximately 2.6 $FEV_1$% at age 6 years between those who were under −1 z-score for weight and those over 0 at age 2 years. The magnitude of association observed in our paediatric UK and Canadian datasets is smaller than previous studies. This may reflect a higher proportion of children diagnosed by newborn screening, or more aggressive nutritional intervention informed by these previous studies.

### 4.1. Strength and limitations

This study has several strengths. First, this study made use of data from two large national CF registries, both with near complete coverage and data collected over 16 years. Using measurements from the same children over time meant that within-patient change could be distinguished from secular trends. This increased the reliability and generalisability of the results [21]. Previous studies used categories to summarise differences in weight, which results in a loss of information. Our study made use of a flexible method for individual level trajectories of weight-for-age and BMI which avoids the known pitfalls of categorising continuous measures [10,22,23]. We also included a range of important potential confounders, including newborn screening, age at diagnosis, geno-

type class and socio-economic status (UK only). We did not include infections of the lung age 1 to 5 years as we hypothesised that these could be on the causal pathway between early growth and later lung function.

We favoured the use of the British 1990 growth reference rather than the combined World Health Organisation and British 1990 reference (UK-WHO) [16], which is currently used by health practitioners in the UK. The UK-WHO reference has a discontinuity at age 4 years where it changes from the WHO 2006 growth standard, to the British 1990. There is a distinct advantage to using a continuous reference to avoid the discontinuity at age 4, given that the main object of study was growth trajectories from 1 to 5 years of age. Results from the model run with the UK-WHO reference were very similar.

This study also had several limitations. There was some missing data, although those with missing data were not different from the complete cases in any important respect so this should not have had an impact on the conclusions. As with most studies conducted on children, we did not have routinely collected measures of lung function before the age of 5.5 years. Spirometric indices such as $FEV_1$ are often not feasible or practical to collect in preschool children. The association between weight and lung function likely tracks from birth [24,25]. Therefore future studies that include measures of nutritional status and lung function from diagnosis are needed, including birthweight and early life measures of weight. The measurement of lung clearance index to evaluate lung function would be ideal [26]. Further the measures of growth in this study were weight and BMI, which cannot distinguish between fat and fat-free mass. Within pwCF both fat and fat-free mass index have been found to be correlated with FEV1% [27], and these aspects of body composition have been shown to have opposite effects on lung function in adolescent children from the general population [28]. A recent study reported longitudinal measures of arm muscle area in a paediatric cohort [29], a promising method which does not require expensive equipment to measure. A study which linked such longitudinal measures, standardised where possible using relevant standards, with later health outcomes may be able to more clearly define which aspect of weight to target when planning interventions. There were notable differences between the countries, especially since newborn screening was implemented earlier in the UK than in Canada, which may have led to earlier interventions and better growth. Overall, the results were similar and consistent between the two countries, despite these differences. Further comparative analysis, which was not the aim of this work, could identify potentially modifiable factors that lead to better outcomes in one country compared to the other. Finally, the registry data used reflect up to date data and including the year 2016. Nevertheless this data pre-dates the widespread use of 'disease modifying' treatments, which promise to greatly improve health for the majority of people with CF [30] and have the potential to alter childhood growth trajectories.

*4.2. Further work*

Future studies should utilize encounter-based data, in which all visits to clinic are recorded, as this may provide greater precision and be able to account for time-varying treatments. Given that weight is likely to co-evolve from birth along with lung function and other factors (including infections, treatment, and socio-economic status), studies in which lung function is available from an early age, along with birthweight and longitudinal measures of body composition, would be valuable. The extent to which poor nutritional status precedes low lung function could be assessed; as well as the potentially differing associations between aspects of body composition and lung function to better inform interventions aimed at increasing lung function.

Although research studies such as this one can inform practice guidelines, it is beyond the scope of this study to suggest how individual CF practitioners should practice. The results of this study imply that individual trajectories, whether that be standardized against growth curves or calculated for an individual, should be considered irrespective of whether the weight or BMI is below the 10th centile. How much change is clinically relevant would require a different study design, which anchors the specific thresholds for change to clinically meaningful end points.

## 5. Conclusion

Our findings provide evidence that early weight-for-age, specifically at age 1 year, and weight-for-age trajectories across early childhood are associated with later lung function, and that this relationship persists after adjustment for potential confounders. Current guidelines may need to be updated to place less emphasis on a specific cut-off (such as the 10th percentile) and encourage clinical tracking of weight-for-age over time, as well as weight-for-age in early infancy.

## Declaration of Competing Interest

CB, DJ and AM report no conflicts of interest. GD reports personal fees (speaker honoraria) from Vertex pharmaceuticals and Chiesi Limited, unrelated to the current work. SBC reports personal fees and other from Chiesi Pharmaceuticals, non-financial support and other from Vertex outside the submitted work. SS reports personal fees from Chiesi Pharmaceuticals unrelated to the current work.

## CRediT authorship contribution statement

**Amy Macdougall:** Formal analysis, Writing – original draft, Conceptualization, Writing – review & editing. **Deborah Jarvis:** Formal analysis, Writing – original draft, Conceptualization, Writing – review & editing. **Ruth H Keogh:** Conceptualization, Writing – review & editing. **Cole Bowerman:** Writing – review & editing. **Diana Bilton:** Writing – review & editing. **Gwyneth Davies:** Writing – review & editing. **Siobhán B Carr:** Writing – review & editing. **Sanja Stanojevic:** Formal analysis, Writing – original draft, Conceptualization, Writing – review & editing.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2022.09.001.

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