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RESEARCH ARTICLE

**REVISED** Using different methods to process forced expiratory volume in one second (FEV<sub>1</sub>) data can impact on the interpretation of FEV<sub>1</sub> as an outcome measure to understand the performance of an adult cystic fibrosis centre: A retrospective chart review [version 2; referees: 2 approved, 1 approved with reservations]

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**Abstract**

**Background:** Forced expiratory volume in one second (FEV<sub>1</sub>) is an important cystic fibrosis (CF) prognostic marker and an established endpoint for CF clinical trials. FEV<sub>1</sub> is also used in observation studies, e.g. to compare different centre's outcomes. We wished to evaluate whether different methods of processing FEV<sub>1</sub> data can impact on centre outcome.

**Methods:** This is a single-centre retrospective analysis of routinely collected data from 2013-2016 among 208 adults. Year-to-year %FEV<sub>1</sub> change was calculated by subtracting best %FEV<sub>1</sub> at Year 1 from Year 2 (i.e. negative values indicate fall in %FEV<sub>1</sub>), and compared using Friedman test. Three methods were used to process %FEV<sub>1</sub> data. First, %FEV<sub>1</sub> calculated with Knudson equation was extracted directly from spirometer machines. Second, FEV<sub>1</sub> volume were extracted then converted to %FEV<sub>1</sub> using clean height data and Knudson equation. Third, FEV<sub>1</sub> volume were extracted then converted to %FEV<sub>1</sub> using clean height data and GLI equation. In addition, year-to-year variation in %FEV<sub>1</sub> calculated using GLI equation was adjusted for baseline %FEV<sub>1</sub> to understand the impact of case-mix adjustment.

**Results:** Year-to-year fall in %FEV<sub>1</sub> reduced with all three data processing methods but the magnitude of this change differed. Median change in %FEV<sub>1</sub> for 2013-2014, 2014-2015 and 2015-2016 was -2.0, -1.0 and 0.0 respectively using %FEV<sub>1</sub> in Knudson equation whereas the median change was -1.1, -0.9 and -0.3 respectively using %FEV<sub>1</sub> in the GLI equation. A statistically significant p-value (0.016) was only obtained when using %FEV<sub>1</sub> in Knudson equation extracted directly from spirometer machines.

**Open Peer Review**

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<b>version 2</b>		report	report
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- Edward McKone**, St Vincent's Hospital, Ireland
- Pierre-Régis Burgel** , Paris Descartes University, France
- Clive Osmond** , University of Southampton, UK

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**Conclusions:** Although the trend of reduced year-to-year fall in %FEV<sub>1</sub> was robust, different data processing methods yielded varying results when year-to-year variation in %FEV<sub>1</sub> was compared using a standard related group non-parametric statistical test. Observational studies with year-to-year variation in %FEV<sub>1</sub> as an outcome measure should carefully consider and clearly specify the data processing methods used.

### Keywords

Cystic fibrosis, epidemiology, patient outcome assessment, forced expiratory volume

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**Author roles:** **Hoo ZH:** Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Supervision, Validation, Visualization, Writing – Original Draft Preparation; **El-Gheryani MSA:** Data Curation, Investigation, Writing – Review & Editing; **Curley R:** Data Curation, Formal Analysis, Investigation, Writing – Review & Editing; **Wildman MJ:** Conceptualization, Methodology, Project Administration, Supervision, Visualization, Writing – Review & Editing

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**REVISED Amendments from Version 1**

As recommended by Prof McKone, we have used Bland-Altman analyses to compare different reference equations (Knudson vs GLI).

As recommended by Prof Burgel, we have:

1. Performed a sensitivity analysis for the results in [Table 2](#) using only adults aged 18 years and above - we have also done the same for the Bland-Altman analyses that were added following suggestion from Prof McKone
2. Replaced the term "FEV1 decline" with "year-to-year FEV1 variation"

**See referee reports**

## Introduction

Cystic fibrosis (CF) is a multi-system genetic condition but the two main affected organs are lungs (resulting in recurrent infections and respiratory failure) and gastrointestinal tract (resulting in fat malabsorption and poor growth)<sup>1</sup>. Median survival has improved to 45 years, in part because of improvement in care quality<sup>2</sup>. An important quality improvement initiative is benchmarking, which involves identifying high-performing centres and the practices associated with outstanding performance<sup>3-5</sup>. Since forced expiratory volume in one second (FEV<sub>1</sub>) is an important CF prognostic marker<sup>6-9</sup>, it is often used as an outcome measure for benchmarking<sup>3-5,10</sup>.

Different statistical methods of analysing FEV<sub>1</sub> data can yield different results<sup>11</sup>, but there is scant attention paid to the methods of processing FEV<sub>1</sub> data. We previously reported a statistically significant reduction in year-to-year %FEV<sub>1</sub> fall for our CF centre from 2013–2016<sup>12</sup>. We now set out to understand the impact of using different FEV<sub>1</sub> data processing methods on our CF centre's outcome.

## Methods

This is a single-centre retrospective analysis of routinely collected clinical data from 2013–2016. Regulatory approval for the analysis was obtained from NHS Health Research Authority (IRAS number 210313). All adults with CF diagnosed according to the [UK CF Trust criteria](#) aged ≥16 years were included, except those with lung transplantation or on ivacaftor. These treatments have transformative effects on %FEV<sub>1</sub><sup>13-15</sup>, thus may affect the interpretation of year-to-year variation in %FEV<sub>1</sub>.

Demographic data (age, gender, genotype, pancreatic status, CF related diabetes, *Pseudomonas aeruginosa* status), body mass index (BMI) and FEV<sub>1</sub> data were collected by two investigators (HZH and RC / HZH and MEG) independently reviewing paper notes and electronic records. Where data from the two investigators differ, the original data from paper notes or electronic records were reviewed to by both investigators to ensure the accuracy of abstracted data. This process ensures the accuracy of abstracted data and helps avoid potential bias from inaccurate or inconsistent data collection<sup>16</sup>. FEV<sub>1</sub> data were processed with

three different methods prior to analysis. First, %FEV<sub>1</sub> readings (calculated with Knudson equation<sup>17</sup> and available in whole numbers) were directly extracted from spirometer machines. Second, FEV<sub>1</sub> volumes (in litres, to two decimal places) were extracted and clean height data were used to calculate %FEV<sub>1</sub> (as whole numbers) with Knudson equation<sup>17</sup>. Third, FEV<sub>1</sub> volumes (in litres, to two decimal places) were extracted and clean height data were used to calculate %FEV<sub>1</sub> with GLI equation<sup>18</sup> using an [Excel Macro](#) (Microsoft Excel 2013).

Best %FEV<sub>1</sub>, i.e. the highest %FEV<sub>1</sub> reading in a calendar year for each study subject was used for analysis since it is most reflective of the true baseline %FEV<sub>1</sub><sup>19</sup>. Year-to-year %FEV<sub>1</sub> change was calculated by subtracting best %FEV<sub>1</sub> at Year 1 from Year 2 (i.e. negative values indicate fall in %FEV<sub>1</sub> and positive values indicate increase in %FEV<sub>1</sub>). In addition to calculating year-to-year %FEV<sub>1</sub> change using three different FEV<sub>1</sub> data processing methods, %FEV<sub>1</sub> change calculated with GLI equation was also adjusted for baseline %FEV<sub>1</sub> using reference values from Epidemiologic Study of CF (ESCF)<sup>20</sup>. The ESCF study found median %FEV<sub>1</sub> change of -3%/year, -2%/year and -0.5%/year for baseline %FEV<sub>1</sub> ≥100%, 40–99.9% and <40% respectively<sup>20</sup>. Adjusted %FEV<sub>1</sub> change was calculated by subtracting median ESCF %FEV<sub>1</sub> change from actual %FEV<sub>1</sub> change. Thus, an adjusted %FEV<sub>1</sub> change >0 meant the subject's year-to-year change in %FEV<sub>1</sub> was less than expected (indicating better health outcome) whilst an adjusted %FEV<sub>1</sub> change <0 meant the subject's year-to-year change in %FEV<sub>1</sub> was more than expected (indicating worse health outcome).

%FEV<sub>1</sub> change from 2013–2014 to 2015–2016 calculated using different FEV<sub>1</sub> data processing methods were compared using Friedman test. Bland-Altman analyses<sup>21</sup> were also used to compare year-to-year variation in FEV<sub>1</sub> as calculated with Knudson equation against year-to-year variation in FEV<sub>1</sub> as calculated with GLI equation, to understand the impact of using different reference equations. Analyses were performed using [SPSS v24](#) (IBM Corp) and [Prism v7](#) (GraphPad Software). P-value <0.05 was considered statistically significant.

## Results

This analysis included 208 adults, with 147 adults providing data for all four years. Overall, the cohort was ageing but baseline %FEV<sub>1</sub> increased from 2014 onwards (see [Table 1](#)).

The %FEV<sub>1</sub> increase was in part due to younger adults with higher %FEV<sub>1</sub> transitioning from paediatric care because %FEV<sub>1</sub> tended to decline from year to year (see [Table 2](#)). However, different year-to-year change in %FEV<sub>1</sub> results were obtained with different FEV<sub>1</sub> data processing methods. There was statistically significant reduction in year-to-year fall in %FEV<sub>1</sub> using %FEV<sub>1</sub> readings as recorded in spirometer machines ( $p=0.016$ ). Cleaning of height data and standardisation of %FEV<sub>1</sub> calculation with Knudson equation<sup>17</sup> did not alter the magnitude of year-to-year variation in %FEV<sub>1</sub>, but the p-value was no longer statistically significant ( $p=0.062$ ). The use of

**Table 1. Characteristics of study subjects from 2013 to 2016.**

	2013	2014	2015	2016
Excluded				
Lung transplantation, n	6	6	9	7
On ivacaftor, n	7	7	9	13
<b>Included, n</b>	<b>166</b>	<b>170</b>	<b>185</b>	<b>186</b>
Age in years, median (IQR)	25 (19 – 31)	26 (20 – 32)	27 (20 – 34)	27 (21 – 34)
Female, n (%)	76 (45.8)	80 (47.1)	87 (47.0)	90 (48.4)
Genotype status: <sup>¶</sup>				
≥1 unknown mutation(s), n (%)	11 (6.6)	13 (7.6)	16 (8.6)	15 (8.1)
≥1 class IV-V mutation(s), n (%)	26 (15.7)	29 (17.1)	36 (19.5)	34 (18.3)
Homozygous class I-III, n (%)	129 (77.7)	128 (75.3)	133 (71.9)	137 (73.7)
Pancreatic insufficient, <sup>†</sup> n (%)	137 (82.5)	135 (79.4)	142 (76.8)	145 (78.0)
CF related diabetes, <sup>‡</sup> n (%)	39 (23.5)	42 (24.7)	42 (22.7)	54 (29.0)
<i>P. aeruginosa</i> status: <sup>§</sup>				
No <i>P. aeruginosa</i> , n (%)	60 (36.1)	57 (33.5)	74 (40.0)	78 (41.9)
Intermittent <i>P. aeruginosa</i> , n (%)	37 (22.3)	36 (21.2)	31 (16.8)	29 (15.6)
Chronic <i>P. aeruginosa</i> , n (%)	69 (41.6)	77 (45.3)	80 (43.2)	79 (42.5)
BMI, median (IQR)	22.3 (19.7 – 24.6)	22.7 (20.0 – 25.0)	23.0 (20.3 – 26.0)	23.2 (20.4 – 26.0)
Best %FEV <sub>1</sub> , median (IQR)	78.7 (54.1 – 92.5)	76.6 (54.4 – 89.7)	77.8 (60.4 – 89.0)	78.5 (58.5 – 89.6)

<sup>¶</sup> Genotype status as defined by international consensus<sup>22</sup>. Homozygous class I-III mutations indicate 'severe genotype'.

<sup>†</sup> Pancreatic insufficiency was diagnosed by the clinical team on the basis of ≥2 faecal pancreatic elastase levels <200µg/g stool and symptoms consistent with maldigestion and malabsorption, in accordance to the [UK Cystic Fibrosis \(CF\) Trust guideline](#).

<sup>‡</sup> CF related diabetes was diagnosed by the clinical team on the basis of oral glucose tolerance test and continuous subcutaneous glucose monitoring results, in accordance to the [UK CF Trust guideline](#).

<sup>§</sup> *Pseudomonas aeruginosa* status was determined according to the Leeds criteria<sup>23</sup>.

**Table 2. Discrepancies in year-to-year %FEV<sub>1</sub> variation with different methods of processing forced expiratory volume in one second (FEV<sub>1</sub>) data.**

Methods of processing FEV <sub>1</sub> data:	Change in %FEV <sub>1</sub> , median (IQR)			Friedman test p-values
	2013 to 2014 (n = 158)	2014 to 2015 (n = 162)	2015 to 2016 (n = 176)	
(1) %FEV <sub>1</sub> (calculated with Knudson equation) extracted from spirometer machines used for analysis <sup>†</sup>	-2.0 (-6.0 to 1.0)	-1.0 (-3.3 to 2.0)	0.0 (-3.0 to 2.0)	0.016
(2) FEV <sub>1</sub> volume (in L) extracted and height data were cleaned, then %FEV <sub>1</sub> calculated using Knudson equation <sup>‡</sup>	-2.0 (-5.0 to 1.0)	-1.0 (-4.0 to 1.0)	0.0 (-3.8 to 2.0)	0.062
(3) FEV <sub>1</sub> volume (in L) extracted and height data were cleaned, then %FEV <sub>1</sub> calculated using GLI equation <sup>§</sup>	-1.1 (-4.6 to 1.5)	-0.9 (-3.2 to 1.5)	-0.3 (-2.9 to 1.8)	0.135
(4) FEV <sub>1</sub> volume (in L) extracted and height data were cleaned, then %FEV <sub>1</sub> calculated using GLI equation, then change %FEV <sub>1</sub> adjusted for baseline %FEV <sub>1</sub> using ESCF reference values <sup>§</sup>	0.7 (-2.4 to 3.6)	1.1 (-1.4 to 3.5)	1.6 (-1.3 to 3.7)	0.210

ESCF - Epidemiologic Study of cystic fibrosis

<sup>†</sup> The vast majority of the %FEV<sub>1</sub> data were from spirometer machines at the Sheffield Adult cystic fibrosis (CF) centre, which were calculated with Knudson equation<sup>17</sup> in whole numbers. Some %FEV<sub>1</sub> data were from spirometer machines at the Pulmonary Function Unit which operationalised the Knudson equation differently; by calculating age to one decimal place to determine the predicted FEV<sub>1</sub>. These spirometer machines also provided %FEV<sub>1</sub> to two decimal places, but this was rounded to whole numbers for the purpose of analysis. These results were presented at the 2017 North American CF Conference and were published as an abstract in *Pediatric Pulmonology*<sup>12</sup>.

<sup>‡</sup> FEV<sub>1</sub> volumes were available in litres to two decimal places from spirometer machines. Height data were also extracted to allow the calculation of predicted FEV<sub>1</sub>. This led us to uncover the inconsistency recording of height, which affected 30–40% of the study subjects and would have introduced erroneous variability to the %FEV<sub>1</sub> because all equations for predicted %FEV<sub>1</sub> are dependent on height. Height data were cleaned to weed out error. Where there was uncertainty regarding the height, the higher value was used to obtain a conservative estimate of %FEV<sub>1</sub>. To replicate calculation process of the spirometer machines at the Sheffield Adult CF centre, age was rounded down to a whole number and predicted FEV<sub>1</sub> in volume were calculated to two decimal places using Knudson equation<sup>17</sup>. This was used to derive the %FEV<sub>1</sub>, which was then rounded to whole numbers for the purpose of analysis.

<sup>§</sup> FEV<sub>1</sub> and height data were extracted as above. %FEV<sub>1</sub> was calculated using the GLI equation<sup>18</sup> using an Excel Macro available at the [European Respiratory Society website](#).

<sup>§</sup> %FEV<sub>1</sub> calculated using the GLI equation<sup>18</sup> as described above, then adjusted for baseline %FEV<sub>1</sub> as described in the 'Methods' section. An adjusted %FEV<sub>1</sub> change of >0 meant the subject's year-to-year fall in %FEV<sub>1</sub> was less than expected for his / her baseline %FEV<sub>1</sub>, indicating better health outcomes.

GLI equation altered the magnitude of year-to-year variation in %FEV<sub>1</sub> although the trend of reduced year-to-year fall in %FEV<sub>1</sub> persisted ( $p=0.135$ ). Adjustment for baseline %FEV<sub>1</sub> further increased the p-value ( $p=0.210$ ).

Similar results were obtained when restricting the analyses to those aged  $\geq 18$  years (see Table 3). Bland-Altman analyses comparing year-to-year variation in %FEV<sub>1</sub> calculated from clean FEV<sub>1</sub> data using Knudson equation<sup>17</sup> vs year-to-year variation in %FEV<sub>1</sub> calculated from clean FEV<sub>1</sub> data using GLI equation<sup>18</sup> indicate the tendency for Knudson equation<sup>17</sup> to over-estimate the magnitude of year-to-year fall in %FEV<sub>1</sub> by a mean difference of 0.1–0.4% (see Figure 1).

**Dataset 1. Sheffield forced expiratory volume in one second (FEV<sub>1</sub>) data**  
<http://dx.doi.org/10.5256/f1000research.14981.d205603>

**Discussion**

We demonstrated that different centre-level year-to-year variation in %FEV<sub>1</sub> results were obtained using different FEV<sub>1</sub> data processing methods. In particular, year-to-year fall in %FEV<sub>1</sub> was smaller in magnitude when %FEV<sub>1</sub> was calculated using GLI equation<sup>18</sup> instead of Knudson equation<sup>17</sup>. This is in part due to the demographic of our centre which has a relatively young adult population. A previous study found a near-linear %FEV<sub>1</sub> decline from childhood to adulthood with GLI equation, whereas there was accelerated %FEV<sub>1</sub> decline during adolescence and young adulthood when %FEV<sub>1</sub> was calculated with Knudson equation<sup>24</sup>. One advantage of using the GLI equation, which is seamless across all ages, is that it improves the interpretation of %FEV<sub>1</sub> decline<sup>24,25</sup>. Another advantage is that %FEV<sub>1</sub> decline can be adjusted for baseline %FEV<sub>1</sub> using

ESCF reference values (since the ESCF values for %FEV<sub>1</sub> decline were calculated using the GLI equation<sup>20</sup>).

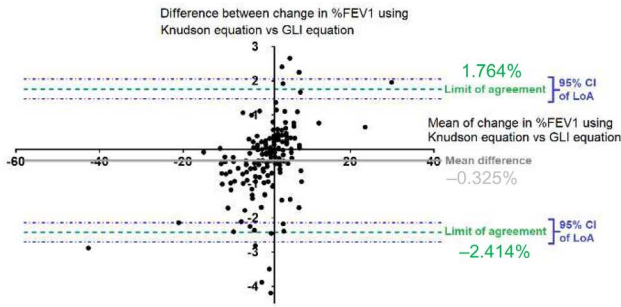
The limitation for all single-centre analysis is the potential lack of generalisability. Another limitation of our analysis is that the ESCF reference values used to adjust year-to-year variation in %FEV<sub>1</sub> were derived using a cohort from around 15 years ago<sup>20</sup>, and may not represent the current population. Our results nonetheless highlighted that year-to-year variation in %FEV<sub>1</sub> can be extremely sensitive to the FEV<sub>1</sub> data processing methods. This is one of the challenges of using year-to-year variation in %FEV<sub>1</sub> to infer quality of care. Another challenge is that %FEV<sub>1</sub> lacks sensitivity as an outcome measure. A recent sample size estimation using the UK CF registry data suggests that 273 adults per centre are needed to detect a 5% FEV<sub>1</sub> difference at the 95% significance level<sup>26</sup>. The sensitivity of measures used to detect variations in care quality is particularly pertinent to CF because a relatively small population is spread across many centres. Indeed, only 6/28 (21.4%) of all UK adult CF centres have  $\geq 273$  adults. That means process measures, e.g. medication adherence, is important to detect variations in quality of CF care. Mant & Hicks previous demonstrated that measuring processes of care proven in randomised controlled trials to reduce death allows detection of meaningful differences in care quality for myocardial infarction with just 75 cases, whereas 8179 cases would be needed if mortality was used as the quality indicator<sup>27</sup>.

Given the limitations of FEV<sub>1</sub> as an outcome measure in CF, results of centre comparisons based on FEV<sub>1</sub> data should be carefully interpreted. Observational studies with year-to-year variation in %FEV<sub>1</sub> as an outcome measure should carefully consider and clearly specify the data processing methods used.

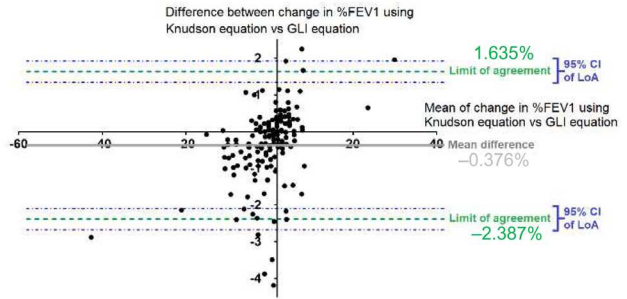
**Table 3. Discrepancies in year-to-year %FEV<sub>1</sub> variation with different methods of processing forced expiratory volume in one second (FEV<sub>1</sub>) data among adults aged  $\geq 18$  years.**

Methods of processing FEV <sub>1</sub> data:	Change in %FEV <sub>1</sub> , median (IQR)			Friedman test p-values
	2013 to 2014 (n = 147)	2014 to 2015 (n = 157)	2015 to 2016 (n = 172)	
(1) %FEV <sub>1</sub> (calculated with Knudson equation) extracted from spirometer machines used for analysis	-2.0 (-6.0 to 1.0)	-1.0 (-3.0 to 2.0)	0.0 (-3.0 to 2.0)	0.016
(2) FEV <sub>1</sub> volume (in L) extracted and height data were cleaned, then %FEV <sub>1</sub> calculated using Knudson equation	-2.0 (-5.0 to 1.0)	-1.0 (-4.0 to 1.0)	0.0 (-3.8 to 2.0)	0.029
(3) FEV <sub>1</sub> volume (in L) extracted and height data were cleaned, then %FEV <sub>1</sub> calculated using GLI equation	-1.3 (-4.6 to 1.3)	-1.0 (-3.2 to 1.4)	-0.3 (-2.9 to 1.8)	0.090
(4) FEV <sub>1</sub> volume (in L) extracted and height data were cleaned, then %FEV <sub>1</sub> calculated using GLI equation, then change %FEV <sub>1</sub> adjusted for baseline %FEV <sub>1</sub> using ESCF reference values	0.5 (-2.4 to 3.3)	1.0 (-1.4 to 3.4)	1.6 (-1.3 to 3.7)	0.149

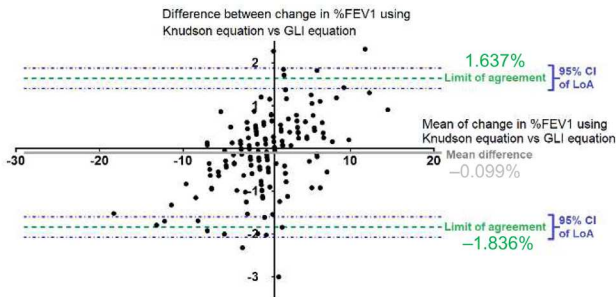
**Change in %FEV<sub>1</sub> from 2013 to 2014 for all adults**



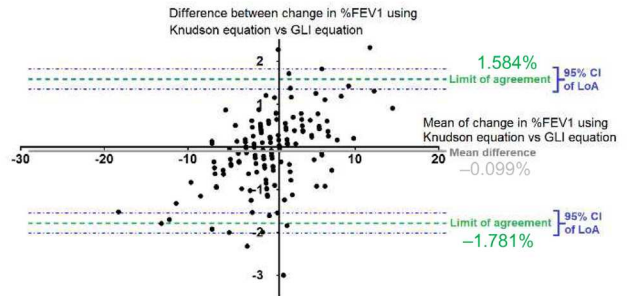
**Change in %FEV<sub>1</sub> from 2013 to 2014 for adults ≥18 years**



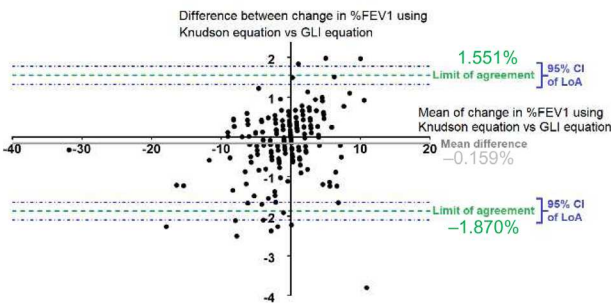
**Change in %FEV<sub>1</sub> from 2014 to 2015 for all adults**



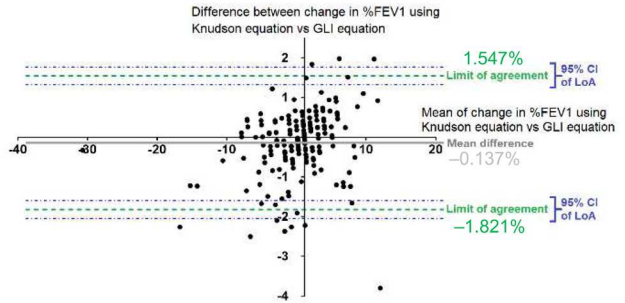
**Change in %FEV<sub>1</sub> from 2014 to 2015 for adults ≥18 years**



**Change in %FEV<sub>1</sub> from 2015 to 2016 for all adults**



**Change in %FEV<sub>1</sub> from 2015 to 2016 for adults ≥18 years**



**Figure 1.** Bland-Altman plots comparing year-to-year variation in %FEV<sub>1</sub> as calculated with Knudson equation (i.e. “Method 2” for processing FEV<sub>1</sub> data according to Table 2) against year-to-year variation in %FEV<sub>1</sub> as calculated with GLI equation (i.e. “Method 3” for processing FEV<sub>1</sub> data according to Table 2).

**Ethical considerations**

Regulatory approval for the analysis was obtained from NHS Health Research Authority (IRAS number 210313).

**Data availability**

Dataset 1: Sheffield forced expiratory volume in one second (FEV<sub>1</sub>) data [10.5256/f1000research.14981.d205603](https://doi.org/10.5256/f1000research.14981.d205603)<sup>28</sup>

**Competing interests**

No competing interests were disclosed.

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<http://www.doi.org/10.5256/f1000research.14981.d205603>



# Open Peer Review

Current Referee Status:



Version 2

Referee Report 08 November 2018

<https://doi.org/10.5256/f1000research.17436.r39259>



**Clive Osmond** 

MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, UK

Thank you for sending me this interesting note. A few thoughts on the analysis from a statistician

1. It's an interesting, though sobering, fact that between 30 and 40 percent of the machine-entered heights are incorrect. Normally the tendency would be for such errors to obscure, rather than generate, associations. This now-known, high error rate makes it less interesting to explore this section of the results.
2. What does a Friedman test measure? It's a non-parametric version of a repeated measures one-way analysis of variance. Two issues are worth considering. It requires a complete table, so only those subjects with all four years of data may be included. Secondly it produces a three degree of freedom test, which is not very well directed to address the most likely question of interest. We might be most interested in detecting a smooth, linear trend over time. However just as much weight is being given to detect non-linear patterns such as curvature {low, high, high, low} and saw-tooth {low, high, low, high}. I don't know how centres are compared officially. Comparison of neighbouring years' data would be unstable. Also, using these non-linear components could be very misleading. I hope that the linear trend is used.
3. Are there any alternative analyses that would address these two issues? Certainly. To begin with, let's use the original data for FEV1% and not worry about their normality. You could fit a mixed model to these data once you stack them in long format ("varstocases" in SPSS). This would enable you to use all data, not just data for those with a complete set. It would also enable you to extract a one degree of freedom test for trend across the four years. This should be a more powerful approach. I now see that the other referees refer to this as well, though I don't agree that you need to have at least three observations per subject.
4. If you are worried about the normality (though the published quartiles are not that alarming) then two alternatives would be (1) to find a normalising transformation that would apply to the stacked column of FEV1% values, or (2) to use a rank-based transformation ("Fisher-Yates") available in SPSS as "rank y /normal into z."
5. What might be the mathematics underlying any difference in slope obtained by the Knudson and GLLI methods? I have tried to abstract the formulae used by Knudson and by GLLI in deriving the predicted FEV1 that is used in the calculation of FEV1%. For a specific example I have chosen males (slightly more common in this study) aged 25 to 28 years (somewhere near the median age) with height of 175cm (just below mean UK adult height).

The Knudson equation has a functional form

$FEV1 \text{ predicted} = 5.1228 - 0.0292 \cdot \text{age}$ .

$FEV1\% = FEV1 / (FEV1 \text{ predicted})$  can then be differentiated to see how it varies with changes in age and FEV1

However the GLI equivalent is given as point estimates from a Cole-Green LMS fitting procedure. The penalised cubic splines are not given, so no functional form is available.

The **table** shows, just for this combination, how the predicted values compare. Those from Knudson are slightly lower and decrease slightly more rapidly with age. Such differences, and those from other combinations, will work together to determine how FEV1% might be expected to change with age and observed FEV.

**Is the work clearly and accurately presented and does it cite the current literature?**

Yes

**Is the study design appropriate and is the work technically sound?**

Partly

**Are sufficient details of methods and analysis provided to allow replication by others?**

Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**

Partly

**Are all the source data underlying the results available to ensure full reproducibility?**

Yes

**Are the conclusions drawn adequately supported by the results?**

Partly

**Competing Interests:** No competing interests were disclosed.

**Referee Expertise:** Stats

**I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Referee Report 31 October 2018

<https://doi.org/10.5256/f1000research.17436.r37306>



**Pierre-Régis Burgel** 

Pulmonary Department and Adult CF Centre Groupe Hospitalier Cochin-Hotel Dieu, Paris Descartes University, Paris, France

No further comment

**Competing Interests:** No competing interests were disclosed.

**Referee Expertise:** Adult pulmonologist with experience in the care of adults with cystic fibrosis. Researcher.

**I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

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Version 1

Referee Report 17 July 2018

<https://doi.org/10.5256/f1000research.16309.r34826>



**Pierre-Régis Burgel** 

Pulmonary Department and Adult CF Centre Groupe Hospitalier Cochin-Hotel Dieu, Paris Descartes University, Paris, France

The authors performed a retrospective analysis of FEV1% predicted data over 3 years in an adult CF center in the UK. They examined FEV1 decline from year to year by calculating variation in best FEV1 during two consecutive years and examined the impact of using data obtained using Knudson equation (directly extracted from the spirometer or recalculated with the appropriate height) vs. GLI equation. They also performed an adjustment using ESCF data.

The authors concluded that trends in FEV1 decline were robust among methods, although the results were somewhat different using different methods/equations.

The study has some interest in highlighting problems associated with these type of calculations, especially when used for benchmarking (as in the UK).

I have the following comments for improvement:

1. An important drawback of Knudson equation is related to the change of FEV1 in the transition from pediatric to adults. This is why the GLI is nowadays often used in mixed pediatric/adult population. The authors used the UK definition of adults (over 16 years) and suggested that some of the difference in their results between Knudson and GLI data are due to the younger patients in this cohorts. I would be happier if the authors could perform a sensitivity analysis using only patients 18 years and over? This would minimize the Knudson/GLI age bias and would make these results more relevant to the adult centres outside of UK. Looking at Table 1, it seems that only a minority of patients were below 18 years.
2. I think the word FEV1 decline is inappropriate in this manuscript. A year to year variation (even over 3 years) is not a decline. For calculating a decline, you would need multiple data points (at the very least 3 data points) and perform more complicated analyses (e.g., mixed model analysis). I would suggest to remove the word decline from the manuscript as the main goal of the authors did not appear to be FEV1 decline but mostly year to year FEV1 variation which is used for benchmarking in the UK.

**Is the work clearly and accurately presented and does it cite the current literature?**

Yes

**Is the study design appropriate and is the work technically sound?**

Yes

**Are sufficient details of methods and analysis provided to allow replication by others?**

Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**

Partly

**Are all the source data underlying the results available to ensure full reproducibility?**

No source data required

**Are the conclusions drawn adequately supported by the results?**

Partly

**Competing Interests:** No competing interests were disclosed.

**Referee Expertise:** Adult pulmonologist with experience in the care of adults with cystic fibrosis. Researcher.

**I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Author Response 12 Aug 2018

**Zhe Hui Hoo**, University of Sheffield, UK

We thank Prof Burgel for the review and we will iterate the manuscript taking into account the two very useful suggestions, i.e.

1. we will perform a sensitivity analysis for the results in Table 2 using only adults aged 18 years and above
2. we will replace the term "FEV1 decline" with "year-to-year FEV1 variation"

**Competing Interests:** No competing interests were disclosed

Referee Report 06 July 2018

<https://doi.org/10.5256/f1000research.16309.r34828>



**Edward McKone**

Department of Respiratory Medicine, St Vincent's Hospital, Dublin, Ireland

FEV1 as a percent of predicted is widely used as an outcome measure in patients with cystic fibrosis and is one of the metrics used to compare centres or countries in benchmarking exercises. This manuscript presents data showing that differences in data processing and the use of different reference equations used to estimate FEV1 as a percent predicted can result varying estimates of lung disease changes and potentially impact comparisons of centres/countries.

The paper supports the standardization of FEV1 collection and reference equations which is currently in development by CF International Registries. It also highlights that different approaches to data collection can impact the interpretation of statistical analyses.

#### Comments:

Differences in FEV1 percent predicted using different equations is well known (Rosenfeld et al<sup>1</sup> and more recently in the cited UK/US comparison study). For this reason, the GLI have been recently accepted as the standard for most CF registries.

Although year to year subtraction is a method of looking at longitudinal changes, regression methodology is preferable to analyse these changes, especially, as in this case, where you have 3 time points. This also allows to adjust for baseline factors such as lung disease severity.

The method of adjustment for baseline lung function is a bit crude. The medians subtracted are from a US population over 10 years ago and are likely to overestimate lung function decline in this population. In the Morgan et al, J Pediatr 2016 paper cited, the benefits of using this type of adjustment was shown using regression.

Did their statistical approach factor in that these were repeated measures in the same patients?

Bland & Altman plots comparing different reference equations could be considered.

The results suggest that height inaccuracy is impacting the results. As this is a single centre study, it is difficult to determine if this is a more universal problem.

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**Is the work clearly and accurately presented and does it cite the current literature?**

Yes

**Is the study design appropriate and is the work technically sound?**

Partly

**Are sufficient details of methods and analysis provided to allow replication by others?**

Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**

Partly

**Are all the source data underlying the results available to ensure full reproducibility?**

Yes

**Are the conclusions drawn adequately supported by the results?**

Yes

**Competing Interests:** No competing interests were disclosed.

**I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

Author Response 12 Aug 2018

**Zhe Hui Hoo**, University of Sheffield, UK

We thank Prof McKone for the review and we will iterate the manuscript taking into account the suggestion to compare the different reference equations (Knudson vs GLI) using Bland-Altman analysis.

We concur the GLI has been recently accepted as the standard for most CF registries.

We concur that regression analyses is preferable to determine FEV1 decline. As recommended by Prof Burgel, we will replace the term "FEV1 decline" with "year-to-year FEV1 variation" in the revised manuscript.

We concur that the method used to adjust year-to-year FEV1 variation for baseline FEV1 is crude. The displayed data from the ESCF paper is only presented according to the four FEV1 categories, hence our choice of adjustment method. Given the limited number of subjects within the Sheffield dataset, we felt it is more appropriate to use reference values for suitably large datasets instead of simply calculating the predicted %FEV1 change using the Sheffield dataset. There are more recent reference values for FEV1 from the ECFSPR (Boëlle et al, 2012) and Canadian registry (Kim et al, 2018); however those papers do not provide reference values for year-to-year FEV1 variation.

Our statistical method account for repeated FEV1 measures since:

1. by using best FEV1, there is only x1 FEV1 reading per person per year
2. only x1 FEV1 reading per person was used to calculate the year-to-year FEV1 variation

As mentioned in the discussion section, we concur that a single-centre study may not be generalisable. However, inaccurate data recording within routine datasets (e.g. CF registries) is unlikely to be an isolated problem. For example, the letter by Hartley et al (2016) in JCF revealed that 6% of the adults with CF at the Manchester Adult CF Centre had incorrect genotype data recorded in the UK CF registry.

**Competing Interests:** No competing interests were disclosed

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