Investigating the effects of long-term dornase alfa use on lung function using registry data

Newsome S.J. a,*, Daniel R.M. b, Carr S.B. c, Bilton D. d, Keogh R.H. a

a Department of Medical Statistics, London School of Hygiene & Tropical Medicine, London, UK
b Division of Population Medicine, Cardiff University, Cardiff, UK
c Department of Paediatric Respiratory Medicine, Royal Brompton & Harefield NHS Foundation Trust, London, UK
d Faculty of Medicine, National Heart & Lung Institute, Imperial College London, London, UK

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Abstract

Background: Dornase alfa (DNase) is one of the commonest cystic fibrosis (CF) treatments and is often used for many years. However, studies have not evaluated the effectiveness of its long-term use. We aimed to use UK CF Registry data to investigate the effects of one-, two-, three-, four- and five-years of DNase use on lung function to see if the benefits of short-term treatment use are sustained long term.

Methods: We analysed data from 4,198 people in the UK CF Registry from 2007 to 2015 using g-estimation. By controlling for time-dependent confounding we estimated the effects of long-term DNase use on percent predicted FEV1 (ppFEV1) and investigated whether the effect differed by ppFEV1 at treatment initiation or by age.

Results: Considering the population as a whole, there was no significant effect of one-year’s use of DNase; change in ppFEV1 over one year was −0.1% in the treated compared to the untreated (p = 0.51) and this did not change with long-term use. However, treatment was estimated to be more beneficial in people with lower lung function (p < 0.001); those with ppFEV1 < 70% at treatment initiation, showed an increase in lung function over one year that was sustained out to five years. The estimated effect of DNase did not depend on age (p = 0.35).

Conclusions: DNase improved lung function in individuals with reduced lung function, bringing a step-change in lung function, but no change in the slope of decline. There was no evidence for a benefit in lung function in those initiating treatment with ppFEV1 > 70%.

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Keywords: DNase; Long-term treatment effect; Patient registry; UK Cystic Fibrosis Registry

1. Background

First licensed for use in the EU and the US in 1994, dornase alfa (DNase) is now one of the commonest cystic fibrosis (CF) treatments, used by almost 60% of people with CF in the UK in 2016 [1,2]. DNase is a mucolytic treatment administered via a nebulizer, decreasing the viscosity of sputum in the airways, aiming to aid in airway clearance, to improve lung function and decrease pulmonary exacerbations [3].

In a phase III clinical trial, using DNase once or twice daily over twenty-four weeks was shown to improve percent-predicted FEV1 (ppFEV1) [4]. Subsequently, a number of studies have examined the effect of longer-term use of DNase. For example, after 96 weeks of follow-up, treatment was shown to significantly improve ppFEV1 in children aged 6 to 10 [5,6].

Most studies have focused on the absolute effect of DNase on lung function over a specified time period, i.e. on a step-change effect. Its impact on the rate of lung function decline is also important and this has been investigated in two studies. These studies showed that during DNase use the rate of lung function decline was less than the rate of decline in the same
patients prior to starting treatment and also less than the rate of decline in a comparator group of patients who never received treatment [7,8]. Only one study has attempted to evaluate the impact of using DNase for more than two years. This was a matched study with 76 patients where it was found that those receiving treatment over four years had a more gradual slope of decline in ppFEV1 [9].

Until recently in the UK regional guidelines for CF use of DNase varied, but DNase tended to be recommended when a person’s ppFEV1 fell below 80%. However, in 2014 a national policy was approved allowing the use of DNase in anyone over six years of age. Thus, more recently, some centres have begun to routinely initiate DNase when a patient reaches six years of age. These differences in treatment practices provide an opportunity to use the UK CF Registry data to investigate the long-term effects of DNase in a diverse population.

There are, however, some challenges that must be addressed when attempting to use observational data for this purpose. The main issue when estimating treatment effects is confounding by indication, whereby more healthy individuals are less likely to receive treatment. A simple comparison of treated and untreated would therefore typically suggest that even an effective treatment is associated with worse outcomes. A further complexity of Registry data is that as it is longitudinal, not only do confounding variables affect both the outcome of interest and the probability of receiving treatment, but they are also themselves affected by whether the patient was receiving treatment or not in previous years. This issue is known as time-dependent confounding and traditional statistical methods will generally lead to biased results. There are several methods available that can deal with time-dependent confounding [10,11], including inverse probability weighted estimation of marginal structural models, g-computation formula and g-estimation. A recent investigation of the application of these methods using registry data showed that for a continuous outcome, such as lung function, g-estimation appeared to be the most reliable and flexible, in particular by accommodating estimation of treatment effect modification by a time-varying covariate [12].

In this paper, we aimed to use the UK CF Registry to investigate the effects of one-, two-, three-, four- and five-years of DNase use on lung function. Furthermore, we aimed to investigate whether there is evidence that treatment is more effective in younger people, as has previously been reported [7]. We also hypothesised that the effect of DNase may differ depending on lung function, and as such we examined whether there is evidence that the treatment effect is modified by previous measures of lung function.

2. Methods

2.1. UK cystic fibrosis registry

The UK Cystic Fibrosis Registry is a national database managed by the Cystic Fibrosis Trust. Each year people with CF attend an annual assessment at which data are collected on their current health as well as on the treatments they have received in the past year. More details about the registry can be found in the data resource profile [13].

People were eligible for inclusion in the study if they had at least two consecutive years of data in the Registry between 2007 and 2015, had not received DNase prior to 2007, had at least one year of treatment-free data, were at least six years old, had lung function data for at least two consecutive years and had not received a lung transplant. The first visit for everyone was therefore at a time when they were not and had never before received DNase treatment. Follow-up data were collected up to 2015, or were censored at death, transplant or loss to follow-up. If people who started receiving DNase stopped during their follow-up, they were censored at the time they stopped treatment. Fig. 1 shows a flow chart of the number of people included and excluded from the study population.

For this study, the primary outcome was change in lung function expressed as absolute change over time in ppFEV1 calculated using the Global Lung Initiative (GLI) calculations [14]. Secondary analyses with ppFVC and ppPEF25–75 as outcomes were also conducted. All outcomes are observed annually.

As well as previous measures of the outcome and DNase, we also adjusted for the following time-varying variables: annual number of hospital and home IV days, CF centre, other muco-

![Flowchart of people included in analysis](image-url)
active treatments, smoking status, CF related diabetes (CFRD), body mass index (BMI), allergic bronchopulmonary aspergillosis (ABPA) and infections (P. aeruginosa, S. aureus and B. cepacia complex); and the following non-time-varying variables: age, gender, ethnicity and genotype class (as defined by McKone et al) [15]. These were selected from the data collected in the Registry as variables that could affect both lung function and the decision to initiate DNase.

2.2. Statistical methods

In a preliminary exploration of the data, baseline covariates, i.e. those measured at the first visit, were summarised in all patients and separately in the following four subgroups: those who never received DNase, those who received DNase for at least one year, those who received DNase for at least five years, and those who stopped DNase during follow-up. Time-varying covariates were summarised across visits in the following five groups: at a patient's first visit, at subsequent visits among people not receiving DNase, at the first visit when people received DNase, at subsequent visits among people receiving DNase, and at the visit when people stopped receiving DNase. We also performed a univariable linear regression to estimate the crude difference in lung function between those receiving and not receiving treatment.

Data were then analysed using g-estimation to investigate the causal effect of up to five years of DNase use on lung function [16]. A recent paper by Vansteelandt and Sjölander has shown how to implement this method using standard statistical software [17]. Full details of this method can be found in the supplementary material to this paper. Briefly, the method works iteratively by first estimating a one-year treatment effect adjusting for the confounders of this effect, then estimating any additional two-year treatment effect adjusting for the relevant confounders of this effect and so on until the maximum follow-up time of interest (five years in our case). Thus, we obtain five different treatment effect estimates; these are the estimated differences in lung function between those using DNase for $k$ years ($k = 1, \ldots, 5$) and those never receiving treatment, with the time-dependent confounding having been adjusted for at each stage.

Evidence that the treatment effect is modified by age or by previous lung function was investigated by including an interaction term between the relevant variable and DNase use at each visit.

For g-estimation, standard errors used to calculate $p$-values and 95% confidence intervals were estimated using the non-parametric bootstrap approach [18]. All analyses were performed using Stata (version 15.0, Stata Corp, College Station, Texas, USA).

3. Results

Overall, 4,198 people were included in the analysis, with a combined total of 20,923 annual assessments. The median number of follow-up visits per person was 5 (IQR 3–7). During follow-up, 2,384 (56.8%) people received DNase for at least one year, and most people who started using DNase continued to receive it indefinitely, with only 441 (18.5%) people stopping during follow-up. In total, 787 people had five or more consecutive years of DNase use.

Table 1 summarises the variables that were considered as confounders for the main analysis. When looking at this summary of the data, we found that those taking DNase tend to have worse symptoms. This is expected, because those needing treatment are expected to be in worse health. This finding is part of the phenomenon of confounding by indication. Particularly, the mean ppFEV$_1$ measured prior to visits when people were not receiving DNase was 80% compared to 72% prior to the visit when people started to receive DNase. Furthermore, the group who ever received DNase had a higher proportion of people with a high genotype class (76% vs 57%), a higher proportion with CFRD (23% vs 18%) and had more annual IV days (mean annual hospital IV days 10 vs 5, and mean annual home IV days 9 vs 5). Table 1 also summarises the group of people who stopped taking DNase during follow-up, but there were no noticeable differences between this group of people and those who continued to take DNase throughout follow-up.

Results from the univariable analysis (row 1 of Table 2) show that people receiving DNase had lower lung function compared to those not receiving treatment throughout follow-up. For example, at one year those receiving DNase had a lung function on average 7.1% lower than those not receiving treatment (95% CI -8.1% to -6.1%, $p < 0.0001$). Furthermore, the average annual decline in ppFEV$_1$ was 1.0% (95% CI 0.9% to 1.2%) in those not taking DNase compared to 1.3% (95% CI 1.1% to 1.5%) in those receiving DNase.

The results from the causal analysis using g-estimation are shown in Table 2 and Fig. 2. On a population level, we found no significant effect of DNase on ppFEV$_1$, with those on treatment estimated to have an absolute change in lung function of −0.1% over one year compared to someone not receiving treatment (95% CI -0.6% to 0.4%, $p = 0.65$). However, by year two this effect became more pronounced with an estimated difference of −0.7% (95%CI -1.4% to 0.05%, $p = 0.069$), and this trend continued out to year five, when it was estimated that on average receiving treatment for 5 years, compared to never receiving DNase, would result in an absolute change in lung function of −3.3% (95% CI -4.9% to −1.7%, $p < 0.0001$).

We found strong evidence that the effect of treatment differs depending on previous lung function ($p < 0.001$), with beneficial effects seen in those with low lung function. This is illustrated in Fig. 2, where beneficial effects are shown over the 5-year duration for people with baseline ppFEV$_1$ <70%, whereas for those with baseline ppFEV$_1$ >70% the rate of decline was steeper in those receiving treatment. For example, for an individual with baseline ppFEV$_1$ of 40%, initiating DNase was estimated to result in a lung function 1.6% higher after one year (95% CI 0.6% to 2.7%, $p = 0.002$) compared to not initiating DNase. Conversely, for an individual with a baseline ppFEV$_1$ of 80%, initiating DNase was estimated to result in a lung function 0.4% lower after one year (95% CI -0.1% to 0.9%, $p = 0.13$) compared to not initiating DNase.
### Table 1
Descriptive Statistics of Key Variables. Data presented as mean (SD) for continuous variables and n (%) for binary and categorical variables.

#### Demographics (4,198 people)

<table>
<thead>
<tr>
<th></th>
<th>All (n = 4,198)</th>
<th>Never used DNase (n = 1,814)</th>
<th>DNase use ≥ 1 year (n = 2,384)</th>
<th>DNase use ≥ 5 years (n = 787)</th>
<th>Stopped DNase during follow-up (n = 441)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline age (Years)</td>
<td>19.8 (12.7)</td>
<td>21.4 (13.5)</td>
<td>18.7 (11.9)</td>
<td>19.1 (11.2)</td>
<td>21.0 (11.1)</td>
</tr>
<tr>
<td>Female</td>
<td>1923 (45.8)</td>
<td>806 (44.4)</td>
<td>1117 (46.9)</td>
<td>361 (45.9)</td>
<td>210 (47.6)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>4061 (96.7)</td>
<td>1761 (97.1)</td>
<td>2300 (96.5)</td>
<td>758 (96.3)</td>
<td>432 (98.0)</td>
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<tr>
<td>Genotype class</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>2828 (67.4)</td>
<td>1031 (56.8)</td>
<td>1797 (76.1)</td>
<td>629 (79.9)</td>
<td>333 (75.5)</td>
</tr>
<tr>
<td>Low</td>
<td>563 (13.4)</td>
<td>353 (19.5)</td>
<td>210 (8.8)</td>
<td>51 (6.5)</td>
<td>35 (7.9)</td>
</tr>
<tr>
<td>None assigned</td>
<td>153 (3.6)</td>
<td>353 (19.5)</td>
<td>301 (12.6)</td>
<td>80 (10.2)</td>
<td>56 (12.7)</td>
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<tr>
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<td>654 (15.6)</td>
<td>77 (4.2)</td>
<td>76 (3.2)</td>
<td>27 (3.4)</td>
<td>17 (3.9)</td>
</tr>
</tbody>
</table>

#### Longitudinal Data (20,923 observations)

<table>
<thead>
<tr>
<th></th>
<th>First Visit [nobody using DNase] (n = 4,198)</th>
<th>Visits where not using DNase (n = 12,194)</th>
<th>First year using DNase (n = 2,384)</th>
<th>Subsequent years using DNase (n = 5,904)</th>
<th>Year after stopping DNase (n = 441)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous ppFEV₁</td>
<td>80.1 (20.9)</td>
<td>72.0 (21.8)</td>
<td>67.1 (21.9)</td>
<td>66.8 (22.6)</td>
<td></td>
</tr>
<tr>
<td>Annual change in ppFEV₁</td>
<td>−1.0 (9.9)</td>
<td>−0.4 (12.5)</td>
<td>−1.6 (9.5)</td>
<td>−1.7 (9.5)</td>
<td></td>
</tr>
<tr>
<td>Previous ppFVCᵇ</td>
<td>90.1 (17.1)</td>
<td>84.5 (18.4)</td>
<td>81.4 (18.6)</td>
<td>81.3 (19.0)</td>
<td></td>
</tr>
<tr>
<td>Annual change in ppFVCᵇ</td>
<td>−0.7 (10.1)</td>
<td>−0.3 (12.1)</td>
<td>−1.2 (10.1)</td>
<td>−1.3 (9.8)</td>
<td></td>
</tr>
<tr>
<td>Previous ppFEF₂₅₋₇₅ᶜ</td>
<td>71.4 (31.2)</td>
<td>63.9 (30.1)</td>
<td>58.1 (27.4)</td>
<td>59.3 (32.8)</td>
<td></td>
</tr>
<tr>
<td>Annual change in ppFEF₂₅₋₇₅ᶜ</td>
<td>−1.3 (21.7)</td>
<td>0.1 (26.7)</td>
<td>−1.0 (19.4)</td>
<td>−5.4 (22.9)</td>
<td></td>
</tr>
<tr>
<td>BMI (z-score)</td>
<td>0.13 (1.14)</td>
<td>0.29 (1.18)</td>
<td>0.00 (1.13)</td>
<td>−0.02 (1.14)</td>
<td>−0.02 (1.20)</td>
</tr>
</tbody>
</table>

#### Infections

<table>
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<tr>
<th></th>
<th>P. aeruginosa</th>
<th>S. aureus</th>
<th>B. cepacia complex</th>
<th>ABPA</th>
<th>CFRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>2453 (58.4)</td>
<td>7170 (58.8)</td>
<td>334 (2.7)</td>
<td>857 (5.1)</td>
<td>2226 (53.0)</td>
</tr>
<tr>
<td>Occasional</td>
<td>33 (0.8)</td>
<td>126 (1.0)</td>
<td>256 (2.1)</td>
<td>69 (0.6)</td>
<td>1038 (24.7)</td>
</tr>
<tr>
<td>&lt;1 packet per day</td>
<td>49 (1.2)</td>
<td>256 (2.1)</td>
<td>256 (2.1)</td>
<td>69 (0.6)</td>
<td>1038 (24.7)</td>
</tr>
<tr>
<td>≥ 1 packet per day</td>
<td>20 (0.5)</td>
<td>69 (0.6)</td>
<td>69 (0.6)</td>
<td>69 (0.6)</td>
<td>200 (4.8)</td>
</tr>
<tr>
<td>Missing</td>
<td>1038 (24.7)</td>
<td>1176 (9.6)</td>
<td>1176 (9.6)</td>
<td>1176 (9.6)</td>
<td>200 (4.8)</td>
</tr>
</tbody>
</table>

#### Smoker

<table>
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<tr>
<th></th>
<th>No</th>
<th>Occasionally</th>
<th>&lt;1 packet per day</th>
<th>≥ 1 packet per day</th>
<th>Missing</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>3058 (72.8)</td>
<td>126 (1.0)</td>
<td>256 (2.1)</td>
<td>69 (0.6)</td>
<td>1038 (24.7)</td>
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<tr>
<td>Occasional</td>
<td>33 (0.8)</td>
<td>126 (1.0)</td>
<td>256 (2.1)</td>
<td>69 (0.6)</td>
<td>1038 (24.7)</td>
</tr>
<tr>
<td>&lt;1 packet per day</td>
<td>49 (1.2)</td>
<td>256 (2.1)</td>
<td>256 (2.1)</td>
<td>69 (0.6)</td>
<td>1038 (24.7)</td>
</tr>
<tr>
<td>≥ 1 packet per day</td>
<td>20 (0.5)</td>
<td>69 (0.6)</td>
<td>69 (0.6)</td>
<td>69 (0.6)</td>
<td>200 (4.8)</td>
</tr>
<tr>
<td>Missing</td>
<td>1038 (24.7)</td>
<td>1176 (9.6)</td>
<td>1176 (9.6)</td>
<td>1176 (9.6)</td>
<td>200 (4.8)</td>
</tr>
</tbody>
</table>

#### Other characteristics

<table>
<thead>
<tr>
<th></th>
<th>P. aeruginosa</th>
<th>S. aureus</th>
<th>B. cepacia complex</th>
<th>ABPA</th>
<th>CFRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>2453 (58.4)</td>
<td>7170 (58.8)</td>
<td>334 (2.7)</td>
<td>857 (5.1)</td>
<td>2226 (53.0)</td>
</tr>
<tr>
<td>Yes</td>
<td>504 (12.0)</td>
<td>2150 (17.6)</td>
<td>550 (23.1)</td>
<td>274 (1.5)</td>
<td>504 (12.0)</td>
</tr>
<tr>
<td>Missing</td>
<td>1468 (35.0)</td>
<td>2588 (21.2)</td>
<td>547 (19.9)</td>
<td>274 (1.5)</td>
<td>504 (12.0)</td>
</tr>
</tbody>
</table>

### Footnotes

-ᵃ Genotype class as defined by McKone et al. [15].
-ᵇ FVC data based on 20,714 observations.
-ᶜ FEF₂₅₋₇₅ data based on 3320 observations.
-ᵈ First visit, so no previous measures available.
The results from the g-estimation analysis provide information on whether any impact of DNase on lung function is in the form of a step change or whether the treatment modifies the slope of decline. In the groups for which we found a beneficial effect of treatment, the results were consistent with DNase resulting in a one-off step change in lung function, rather than a change in overall trajectory. Full results can be seen in Table 2, but taking individuals who start treatment with a baseline ppFEV₁ of 40% as an example, the estimated difference in population average effect by baseline ppFEV₁ of 40% is 0.4%. This effect decreased with each year of treatment, but was still significant at 5 years, with an estimated difference of 0.1%.

Estimated change in effect per 10% change in baseline ppFEV₁

<table>
<thead>
<tr>
<th>Years of DNase use</th>
<th>Est</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
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</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
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</tr>
</tbody>
</table>

We used UK CF Registry data to estimate long-term effects of DNase use, controlling for confounding by indication by using state-of-the-art statistical methodology not previously applied to CF registry data. In our study, for individuals with a reduced lung function and not using DNase, we have shown that initiating DNase treatment and using it for one year brings a benefit such that ppFEV₁ is higher after one year than it would have been had those individuals not initiated DNase treatment. This beneficial effect appeared to remain with continued use of DNase out to five years, but with no overall modification of the lung function trajectory, as the estimated effect remained stable between years one and five.

One reason why it is important to estimate long-term effects of treatment is to see if a treatment modifies overall lung-function trajectory or just provides a one-off increase [19,20]. Fig. 3 shows two hypothetical lung-function trajectories for an individual treated with DNase compared to the lung-function trajectory of someone not receiving treatment. These trajectories show how treatment could either be disease modifying, where the lung function of those receiving treatment continues to grow wider apart from the lung function of those not receiving treatment, or alternatively how the overall lung-function trajectory could remain unchanged after an initial increase.

Crude comparisons between those who received and did not receive DNase clearly indicate that there is confounding by indication, such that individuals taking DNase tend to have worse health status than those not taking DNase. If this is not appropriately handled in the analysis, any estimates of the treatment effect would not have a causal interpretation. In this study, we made use of appropriate statistical methods to address the confounding by indication, accounting for the longitudinal setting, thereby showing how registries can be used to evaluate the long-term effects of treatment. Randomised controlled trials (RCT) are the gold standard for establishing treatment efficacy, but as previously discussed, it is preferable for a CF treatment to alter lung function trajectory rather than to provide a one-off improvement, and assessing change in trajectory requires longer follow-up than would typically be feasible in trials [21]. The analyses used in this paper take advantage of clear heterogeneity in treatment practices as the proportion of patients receiving DNase at individual CF centres ranges from <20% to >80% [2]. As the groups who receive and do not receive DNase include individuals with wide-ranging clinical characteristics, the statistical methods used in this paper can correct for confounding by indication as long as data on all confounders have been collected. We were able to adjust for a large number of variables using the data available in the UK CF Registry data.
Registry, but it is not possible to verify whether confounding by indication has ever been completely dealt with and the causal interpretation of our results therefore depends on the assumption of no unmeasured confounding [22].

A previous registry study by Hodson et al. of the European Epidemiologic Registry of Cystic Fibrosis estimated a one-year treatment effect of DNase on ppFEV1 of 3.6% (95% CI 1.8% to 5.3%) and a two-year treatment effect of 2.5% (0.7% to 4.4%) [7]. These are larger population-average treatment effect estimates than obtained in our study, but the population for those studies had lower average baseline ppFEV1, who were the patients we found benefitted most from treatment.

Only two previous studies have investigated the effects of DNase in people with ppFEV1 > 80% and only one of these

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**Fig. 2.** Estimated mean difference in the change in ppFEV1 between dornase alfa users compared to non-users (dashed grey line), by years of treatment. The top-left figure shows the estimated overall average population effect, with the remaining figures highlighting the differential effects based on ppFEV1 at treatment initiation. The horizontal dashed grey line is the line indicating no treatment effect.

**Fig. 3.** Examples of possible lung function trajectories depending on treatment effect through time.
included lung function as an outcome [23,24]. That study only administered DNase for four weeks and found no effect of treatment on ppFEV1; treatment effect 0.1% increase in ppFEV1 [24]. In our study, for individuals with higher lung function, those on DNase treatment had steeper trajectories of lung function decline than comparable individuals not receiving treatment. This may suggest that it would be more beneficial, in terms of lung function outcomes, to wait until lung function starts to decline before initiating DNase. However, as with all observational studies, it is possible that unobserved confounders affect these results. With the rich Registry data, we believe we have accounted for the covariates that could affect both lung function and the probability of receiving DNase treatment to account for confounding by indication, but it is possible that there are some unmeasured health-related variables that affected the decisions to initiate treatment in these individuals. For example, although an individual may have had a high lung function measurement at the previous annual assessment, they may have been beginning to show signs of lung function deterioration that was not picked up by having only one lung function measure per year.

Upon initiation of DNase, most people continue to receive the treatment indefinitely, with only very small numbers of people stopping treatment. Due to this, with the sample size available, it was not possible to estimate the effect of stopping treatment. However, as we observed that treatment only appeared to be beneficial in individuals with reduced lung function, future studies could investigate whether treatment needs to be continued in people who recover to higher levels of lung function.

A major strength of this study is the use of the UK CF Registry data, which are collected at regular intervals according to a standardised protocol. The data include a large number of variables that we could account for as potential confounders. One of the main limitations of this study is that there are no data available on levels of adherence to treatment. It is known to be particularly hard to measure adherence levels, but previous studies have estimated that average adherence levels to nebulised therapies, such as DNase, may range between 60% and 70% [25,26]. Specifically, for a longitudinal study, we may expect adherence levels to be higher at treatment initiation and decrease through time, which may partly explain why the observed effects are not as pronounced as in RCT, where adherence would typically be higher [27].

The UK CF Registry contains data on over 99% of people with CF in the UK, but a large number of these people were excluded from this analysis. The majority of these exclusions were due to people who were already receiving DNase prior to 2007 or people aged under six, and this is not considered to be a source of bias. Our results are applicable to people aged over six and estimate the effects of the first five years of DNase use. The method of g-estimation relies on having equally spaced visits, and therefore a number of people were censored due to missing lung function measurements during follow-up. We used so-called ‘censoring weights’ within g-estimation, which reweights individuals who remain in the study to account for those lost to follow-up.

The analyses presented in this paper use the FEV1 measure obtained on the date of a patient’s annual review. An alternative approach would be to use the best FEV1 measure obtained since the last annual review. However, best FEV1 has only been collected in the UK CF Registry since 2012 and the aim of this paper, to estimate the effects of long-term DNase use, would not be possible with the number of best FEV1 observations available. The unknown timing of the best FEV1 measure relative to the other measures would also present additional challenges for the analysis. According the Registry protocol, annual reviews take place at a time when the patient is stable, and ongoing validation procedures indicate good adherence to this protocol [28]. Furthermore, there is no evidence to suggest that those receiving DNase are more likely to have their annual review during an unstable period compared to those not receiving DNase, meaning that using the FEV1 measure obtained during the annual assessment should not result in any bias.

It is also acknowledged that spirometry measures, such as FEV1, may not be sufficiently sensitive to detect the early stages of lung function decline, and it has been suggested that other measures such as lung clearance index (LCI) may give a better indication of early lung function deterioration [29,30]. Unfortunately, LCI is not collected in the UK CF Registry, so it was not possible to investigate this. However, FEF25–75 is collected in the registry, albeit less reliably than FEV1 (3320 FEF25–75 measurements compared to 20,923 FEV1 measurements in this analysis), and the results showed similar findings to the findings with FEV1, but with much larger confidence intervals, reflecting the lack of measurements and increased variability of this measure (see Supplement).

In conclusion, we have shown a beneficial long-term effect of DNase in people with reduced lung function, but with no overall change in lung-function trajectory. There is a differential effect of treatment based on lung function at treatment initiation with no improvements in lung function seen in individuals initiating treatment with ppFEV1 higher than 70%. Finally, this study highlights the potential of registries in investigating the effects of long-term treatment use and that issues of confounding-by-indication can be addressed with appropriate statistical methods.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcf.2018.08.004.

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