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**Does presenting with meconium ileus affect the prognosis of children with cystic fibrosis?**

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**Title page****Does presenting with meconium ileus affect the prognosis of children with cystic fibrosis?**

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**Short Title****Meconium ileus and outcome in cystic fibrosis**

## Summary

It is a matter of debate as to what extent the long-term outcome of cystic fibrosis (CF) is affected by presenting with meconium ileus (MI). We compared long-term clinical outcomes of CF children who presented with MI, to those presenting with other symptoms (non-MI) in an era of non new-born-screening (NBS).

We collected annual lung function data between the ages of 8 to 15 years in terms of percent predicted first second forced expired volume (FEV1%pr), percent predicted forced vital capacity (FVC%pr), and between the ages of 2 to 15 years annual height and weight z-scores (HtZ and WtZ respectively) for children attending the Royal Brompton Hospital CF clinic. To be included in the study, subjects had to have at least 5 pulmonary function tests and 5 anthropometric measurements recorded over this period.

38 MI and 76 non-MI subjects were compared. There were no significant differences in genotype, sex, chronic Pseudomonas infection, or pancreatic enzyme use between the 2 groups. The median age of diagnosis was 1 day (MI) vs. 7 months (non-MI). There was a decline in spirometry and anthropometric variables over the study period for both MI and non-MI groups apart from WtZ score in the non-MI group. Mixed model analysis adjusting for potential confounders including genotype, pancreatic status, sex, chronic Pseudomonas aeruginosa lung infection, and age of diagnosis revealed no difference between the 2 groups in terms of lung function and growth during the time period of the study, however there was a non-significant trend for subjects presenting with MI to do better in all 4 parameters.

We conclude that babies presenting with MI have no worse long-term outcome than those presenting symptomatically later in infancy, despite having undergone invasive procedures in the newborn period. This underscores the importance of early diagnosis and treatment in CF.

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**Keywords**

Lung function

Growth

Presentation

New born screening

Survival

For Peer Review

## Introduction

Meconium ileus (MI) is characterised by neonatal intestinal obstruction caused by the accumulation of desiccated and inspissated intraluminal meconium[1]. Around 15% of patients with pancreatic insufficient cystic fibrosis (CF) present with MI [2] but MI is also recorded rarely in normals and pancreatic sufficient CF [3]. It is a matter of debate as to what extent long-term outcome in CF is affected by MI.

Two groups from areas where new born screening (NBS) is established have suggested that patients presenting with MI have a worse prognosis in terms of lung function than those without MI diagnosed through NBS. [4,5,6,7] One of these groups, the Wisconsin group [5,6,7] also found MI patients had poorer growth.

However, 3 studies have suggested that MI patients have the same prognosis as patients presenting with other symptoms, not diagnosed through new-born-screening. Munck et al [8] in 2006 compared 26 children presenting with MI diagnosed with CF at a median age of 1 month to 26 children without MI presenting with other symptoms (unscreened) diagnosed with CF at a median age of 3.5 months. They compared height and weight z scores at 1, 3, 6, 10 and 15 years of age. They also compared forced vital capacity (FVC) and first second forced expired volume (FEV<sub>1</sub>) at 6, 10 and 15 years. There was no difference between the two groups in growth or lung function and they concluded that presenting with MI made no difference to clinical outcome compared to presenting with other symptoms.

The second study [9] compared 158 patients presenting with MI to 1175 CF patients presenting with other symptoms again in a pre-new born screening era. They compared 2 subgroups based on date of birth and showed that MI patients born between 1963 and 1972 had lower weight and height percentiles at age 13 years compared to non-MI patients. However, subjects born between 1973 and 1982 showed no difference in height and weight at 13 years. There were also no differences in FVC, FEV<sub>1</sub>, or forced expiratory flow at 25% to 75% of FVC (FEF<sub>25-75</sub>) in this subgroup. There was a significantly better survival in the later compared to the earlier cohort, particularly in the MI group in

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3 the first year of life. This study suggests that advances in medical care especially in the perinatal period  
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5 improved the prognosis of patients in the MI group.  
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9 The merits of the study by Kerem et al [9] include the large sample size and long time period of the  
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11 study. However, the problem with such a long time period is the changes in medical practice taking  
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13 place in this time. Although the authors tried to limit these differences by analysing the results in 2  
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15 cohorts, this resulted in a lack of pulmonary function test data to power the study.  
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19 The most recent study [10] retrospectively compared 60 CF subjects with a history of MI (mean age of  
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21 diagnosis 0.4 months) to 310 without MI presenting with other symptoms (mean age of diagnosis 21.8  
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23 months). Using a combination of cross-sectional and longitudinal analyses, they showed that there was  
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25 no difference in lung function between the 2 groups. Although this study is more recent, the large age  
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27 range of the study subjects (0-48 years) means that it is highly likely that there was wide variation over  
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29 time in the medical care that the patients received.  
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33 The aim of our single centre study is to test the hypothesis that with current standards of medical care  
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35 and in an era of non-NBS there is no difference in clinical outcome between CF patients presenting  
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37 with MI and patients without MI presenting with other symptoms.  
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41 The question has important practical as well as theoretical implications. If patients presenting with MI  
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43 have the same or better prognosis than those diagnosed later with other symptoms, despite in many  
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45 cases having had to undergo a major abdominal operation, this would be a pointer to the benefits of  
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47 early diagnosis of CF, which has been disputed by some [11]. On the other hand, if they do worse,  
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49 despite modern treatment, this implies that new treatment strategies are needed in this group and that  
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51 they would have potentially more to gain from novel, disease-modifying therapies.  
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## Material and Methods

### Study Subjects:

CF patient data is updated on the Royal Brompton Hospital CF database after the patients' annual review by the CF nurse or secretary. By the 1<sup>st</sup> January 2008, 665 subjects had been registered onto the database since it began in 1986. All had a diagnosis of CF confirmed with a positive sweat test (a chloride value >60mmol/l in two sweat samples) and/or had the presence of two recognised CF disease-causing genetic mutations. Of the 665 subjects 75 of these had presented with meconium ileus and 590 with non meconium ileus (non-MI) symptoms including respiratory symptoms and/or failure to thrive. To be included, subjects had to be at least 15 years old at the time of the study (i.e. born before 1<sup>st</sup> January 1993). Subjects had to have a minimum of 5 recorded annual pulmonary function tests in terms of percent predicted first second forced expired volume (FEV<sub>1</sub>%pr) and percent predicted forced vital capacity (FVC%pr) from the age of 8 years. They were also required to have at least 5 recordings of annual height and weight z-scores (HtZ and WtZ respectively) from the age of 2 years. Pulmonary and anthropometric data was analysed up to and including the 15<sup>th</sup> year of life. Ethical approval was obtained from the Royal Brompton Hospital Research Ethics Committee. From 16 years of age many of the subjects were referred to other adult CF tertiary centres so survival data was the only outcome measure recorded thereafter. These were obtained by telephone contact to the adult tertiary centres to which the children had been referred.

### Study Design:

The primary objective of our study was to test the hypothesis that, in an era of non-NBS there is no difference in clinical outcome between CF patients presenting with MI (MI group) and those without MI presenting with other symptoms (non-MI group). We used a retrospective longitudinal study to compare growth and pulmonary function data of eligible subjects in MI and non-MI groups on a year-by-year basis. Details of treatment protocols can be found at

<http://www.rbht.nhs.uk/healthprofessionals/clinical-depts/paediatrics/childrencf/>

### Methods/Statistical Analysis:

The primary outcomes were annual HtZ /WtZ scores (age 2-15 years) and FVC%pr/ FEV<sub>1</sub>%pr (age 8-15 years). 8 years was taken as the age at which pulmonary function testing could be accurately



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3 reproduced. Pulmonary function was measured using a Jaeger CompactLab pneumotachograph in the  
4 lung function laboratory by trained technicians. FEV<sub>1</sub> and FVC were measured and expressed as  
5 percentages of predicted values obtained from equations based on gender and height by Rosenthal et al  
6 [12]. Weight (minimal underclothing) and height (Harpenden stadiometer) were measured and  
7 expressed as standard deviation scores (Z-scores) using published population means and standard  
8 deviations [13]. Baseline characteristics of the study groups were compared using Chi Squared  
9 analysis with Fisher's exact test for categorical data and Mann-Whitney for continuous data.  
10 Characteristics included sex and age, genotype ( $\Delta F508/\Delta F508$  homozygosity), use of pancreatic  
11 enzymes and presence of chronic *Pseudomonas aeruginosa* in lung secretions (defined as 2 or more  
12 isolations of *Pseudomonas aeruginosa* necessitating the use of long term anti-*Pseudomonas* nebulised  
13 antibiotic inhaled therapy).  
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27 It was calculated [14,15] that in order to detect a mean difference in FEV<sub>1</sub>%pr of 10% between MI and  
28 non-MI groups, a sample size of at least 20 subjects (with each subject having 5 measurements over at  
29 least 5 years i.e. 100 observations) is needed for a 5% significance level at 80% power.  
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35 A random selection of subjects was made from the non-MI group for matched selection purposes by  
36 employing the Excel RAND function to provide approximately a 2:1 non-MI:MI ratio.  
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41 Primary outcomes were analysed using mixed effects regression models REML (restricted maximum  
42 likelihood method). The MI and non-MI groups were compared for each of the main outcomes:  
43 FEV<sub>1</sub>%pr, FVC%pr, HtZ and WtZ over time. The models were adjusted for sex, genotype, age of  
44 diagnosis, pancreatic status and chronic *Pseudomonas aeruginosa* pulmonary status. The statistical  
45 software package STATA version 10.1 was used. Survival in the two groups was compared using  
46 Kaplan-Meier analysis. Graphic representation of the outcomes of lung function and growth was done  
47 using MS Excel with the error bars representing the 5<sup>th</sup> and 95<sup>th</sup> percentiles around median values for  
48 MI and non-MI groups. Subgroup comparison of FEV<sub>1</sub>%pr at the age of 10 years was analysed using  
49 Mann Whitney (SPSS version 12).  
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## Results

From the original 75MI and 590 non-MI subjects registered on the CF database, 38/75 MI subjects were born before 1<sup>st</sup> January 1993 and had sufficient pulmonary function and anthropometric data (median age of diagnosis 1 day) to meet the above criteria. Of these 38, thirty underwent a newborn surgical procedure (14 had intestinal resection), 7 subjects were successfully treated with gastrograffin enemas and 1 passed a meconium plug spontaneously at 19 hours of age. 283/ 590 non-MI subjects met the inclusion criteria. From this population of 283, seventy-six subjects were selected at random to act as controls for the MI population (median age of diagnosis 7 months). 30 of these presented with a history of combined chest problems and failure to thrive, 16 with chest problems alone, 15 failure to thrive alone and 15 with other modes.

The Royal Brompton Hospital CF database contained up to date data for all included subjects. The database is complete in that as far as we are aware, if a patient has been seen in the annual clinic, the data is registered on the database. However, not all included patients had data recorded from each annual review. From the 8-year review onwards, on average lung function data for 86% non-MI and 81% MI patients was recorded annually. From 2 to 8 years, at each review on average only 60% non-MI and 56% MI patients had anthropometric measurements recorded. We believe that missing data is largely due to late referral to the Brompton Hospital and non-attendance at annual appointments.

Since the age of 15, five subjects from the non-MI group have subsequently died compared to none from the MI group (by 1<sup>st</sup> January 2009). This difference was not statistically different. (See figure 1).

There was no significant difference between MI and non-MI groups in terms of genotype, sex, median date of birth and median age of first attendance at annual review clinic (table 1). There was also no difference in chronic *Pseudomonas* colonisation (defined as 2 or more previous sputum isolations of *Pseudomonas aeruginosa* and on long term nebulised anti-*Pseudomonas* antibiotics) or in the median age of first sputum isolation of *Pseudomonas aeruginosa*. There was no significant difference in pancreatic enzyme use. We did not make pancreatic sufficiency an exclusion criteria because, although rare, patients who are pancreatic sufficient can get MI. In order to reflect the CF population, the 6 pancreatic sufficient non-MI patients were therefore included. There was a significant difference,

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3 however, in the median age of commencing pancreatic enzymes (1 day old in the MI group versus 211  
4 days old in the non-MI group,  $p=0.00$ ).

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10 Figures 2 to 5 display graphically how the median values of all 4 primary outcomes vary over time for  
11 both MI and non-MI groups. Figure 2 shows a decline over time for both groups in median FEV1%pr  
12 but the median values are higher in the MI group at all but 1 time point (8 years). Figure 3 shows the  
13 decline over time of median FVC%pr in both groups over the study period but with values higher in the  
14 MI group at all time points. Figure 4 shows the median HtZ score decreasing over the time period of  
15 the study in both groups. Again, the median values are higher at all time points in the MI group **apart**  
16 **from 1 (10 years)**. Figure 5 shows higher median values for WtZ score at all but 2 time points in the MI  
17 group (6 and 12 years), however the overall linear trend is for the median WtZ to decrease in the MI  
18 group but increase in the non-MI group over time.

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31 Table 2 shows a statistical comparison of MI and non-MI groups for all 4 outcomes over the time  
32 period of the study. The mixed effects REML regression model, adjusting for sex, age of diagnosis,  
33 genotype, pancreatic status and presence of chronic Pseudomonas aeruginosa infection and age of  
34 diagnosis showed no statistically significant difference between the 2 groups for all 4 parameters over  
35 the time period of the study. There was a non-statistically significant trend for the FEV1%pr to be  
36 higher on average by 3.36% per year in the MI group compared to the non-MI group. Similar trends  
37 were seen for the other outcome measures (2.87% per year for FVC%pr, 0.06 HtZ per year and 0.01  
38 WtZ per year in favour of the MI group).

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There is a possibility that over the time course of the study prognosis and survival has improved **which**  
**could influence the results**. We therefore compared the FEV1%pr at the age of 10 years between MI  
and non-MI subjects in 2 subgroups, those born < 01/01/1989 and those born between 02/01/1989 and  
01/01/1993. In the earlier subgroup, at the age of 10 years, FEV1 was recorded for 27/33 non-MI  
subjects with a median FEV1%pr of 83%. This was compared to 13/16 MI subjects with a median  
FEV1%pr of 96%. This difference, however, was not statistically significant ( $p=0.260$ , Mann  
Whitney). In the later subgroup, at the age of 10 years, 43/43 non-MI subjects had a median FEV1%pr

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3 of 89%. This compared to 94% in MI subjects (n=20/22). This difference again was not significant  
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5 (p=0.114, Mann Whitney).  
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For Peer Review

## Discussion

Here, we report that during the first 15 years of life there was no statistically significant difference in lung function and growth outcomes between children presenting with meconium ileus and those presenting later with other symptoms during an era of non-NBS. There was a non-significant trend for the prognosis of the MI group to be slightly better than the non-MI group in terms of growth and lung function. This is despite the fact that many of the meconium ileus group had an invasive procedure in the newborn period, which is likely to predispose to acquisition of *Pseudomonas aeruginosa*. [16], (Our results did not demonstrate this however with MI subjects having the same timing of first *Pseudomonas* colonisation and rate of chronic infection as non-MI subjects). The significant difference in the median age of starting pancreatic enzymes (1 day MI versus 211 days non-MI) is most likely a direct result of earlier diagnosis.

There were more deaths in the non-MI group compared to the MI group though this difference was not statistically significant.

The strengths of this study include the longitudinal design, and the fact that anthropometric, lung function measurements and CF treatment after the correction of MI was standardised in a single centre. The main weakness is the study size. The inclusion criteria ensured sufficient longitudinal data to power the study but also meant that the final sample excluded patients with fewer data points. Longer follow-up would have been more ideal but this was difficult due to referral of many patients to other adult tertiary centres. However the fact that up to 15 years after surgery (in the MI group) we could not detect a difference between the two groups in the major prognostic factors (spirometry, nutrition) is reassuring,

There is also the possibility, however, that over the 15-year time course of the study prognosis and survival has improved which could influence the results. However, when 2 subgroups were analysed separately based on year of birth (<01/01/89 or 02/01/89-01/01/93) there was no significant difference in FEV1%pr at age 10 years between MI and non-MI subjects. However, drawing any conclusions from this is difficult due to the small numbers compared.

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5 An alternative study design would be to use a large national database, which would enable larger  
6 numbers to be studied. This approach is not without problems; treatment protocols vary from centre to  
7 centre, and for most if not all databases, there is no attempt to quality control the anthropometric and of  
8 particular importance, the lung function measurements. In a single centre study such as ours there is  
9 careful calibration of equipment and standardisation of measurement techniques.  
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18 Our findings support our original hypothesis that with **current standards of medical care and in an era**  
19 **of non-new born screening**, there is no difference in clinical outcome between CF patients presenting  
20 with MI and patients without MI presenting with other symptoms.  
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26 Our conclusion correlates with that of the study by Munck et al detailed earlier who also compared, on  
27 a smaller scale, MI presenting patients to a non-screened population presenting with other symptoms.  
28 [8]. **It also agrees with the findings of Kappler et al [10], who, over a variable study period, showed no**  
29 **difference in lung function between MI and non-MI non-screened subjects, both on longitudinal and**  
30 **cross-sectional analyses and no difference in nutritional parameters on cross-sectional analysis. Our**  
31 results also correlate with the 2<sup>nd</sup> cohort of patients (diagnosed between 1973 and 1982) in the study by  
32 Kerem et al in which there was no significant difference between MI and non-MI **non-screened** groups  
33 in terms of lung function and growth.  
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43 Our results disagree with those studies comparing MI presenting patients to those without MI  
44 diagnosed by new born screening [4,5,6,7]. These studies have all shown a worse outcome for MI as  
45 compared to non-MI NBS patients. The Wisconsin CF Neonatal Screening Project prospectively  
46 compared 32 MI to 50 non-MI patients diagnosed by NBS from diagnosis to twelve years of age [5,  
47 6,7]. They showed that MI patients had significantly worse lung function as well as growth over the  
48 study period. Evans et al [4] compared 39 MI with 39 non-MI NBS patients at just one time point.  
49 They showed no difference in growth between the two groups but the MI group had significantly worse  
50 FEV1%pr. These studies would suggest that, in these centres at least, either MI per se, or more likely,  
51 the effects of interventions in the newborn period, carry a long-term adverse effect.  
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3 It is recognised by some [17, 18, 19, 20] but not by others [21, 22] that earlier diagnosis is beneficial to  
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5 long term clinical outcome in CF. The likely explanation for our findings differing from findings in  
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7 studies using NBS patients as a control group [4, 5, 6, 7] is that although many of our MI subjects  
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9 required surgery, the earlier diagnosis of the MI group compared to the non-MI group allowed earlier  
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11 institution of CF therapy. This may have offset any possible disadvantage to the MI group of invasive  
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13 interventions in the newborn period. This delay in diagnosis is not as apparent when comparing MI-  
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15 presenting patients to non-MI patients diagnosed soon after birth by NBS.  
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19 In summary, we have shown that within a non-screened population CF patients presenting with MI  
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21 have the same prognosis (up until the age of 15 years) as those presenting later with other symptoms.  
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23 Comparing our results to studies involving non-MI NBS subjects as controls, lends support to the  
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25 benefits of early diagnosis and, indirectly, NBS. Future studies should focus on the outcomes of MI  
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27 patients compared with non-MI patients diagnosed through NBS, to determine if presenting with MI  
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29 truly affects long-term outcome in CF in the modern era of surgery and intensive care. If this is the  
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31 case, there will be a need to focus on improving the peri-operative care of these patients.  
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For Peer Review



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**Title page****Does presenting with meconium ileus affect the prognosis of children with cystic fibrosis?**

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**Short Title****Meconium ileus and outcome in cystic fibrosis**

## Summary

It is a matter of debate as to what extent the long-term outcome of cystic fibrosis (CF) is affected by presenting with meconium ileus (MI). We compared long-term clinical outcomes of CF children who presented with MI, to those presenting with other symptoms (non-MI) in an era of non new-born-screening (NBS).

We collected annual lung function data between the ages of 8 to 15 years in terms of percent predicted first second forced expired volume (FEV1%pr), percent predicted forced vital capacity (FVC%pr), and between the ages of 2 to 15 years annual height and weight z-scores (HtZ and WtZ respectively) for children attending the Royal Brompton Hospital CF clinic. To be included in the study, subjects had to have at least 5 pulmonary function tests and 5 anthropometric measurements recorded over this period.

38 MI and 76 non-MI subjects were compared. There were no significant differences in genotype, sex, chronic *Pseudomonas* infection, or pancreatic enzyme use between the 2 groups. The median age of diagnosis was 1 day (MI) vs. 7 months (non-MI). There was a decline in spirometry and anthropometric variables over the study period for both MI and non-MI groups apart from WtZ score in the non-MI group. Mixed model analysis adjusting for potential confounders including genotype, pancreatic status, sex, chronic *Pseudomonas aeruginosa* lung infection, and age of diagnosis revealed no difference between the 2 groups in terms of lung function and growth during the time period of the study, however there was a non-significant trend for subjects presenting with MI to do better in all 4 parameters.

We conclude that babies presenting with MI have no worse long-term outcome than those presenting symptomatically later in infancy, despite having undergone invasive procedures in the newborn period.

This underscores the importance of early diagnosis and treatment in CF.

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**Keywords**

Lung function

Growth

Presentation

New born screening

Survival

For Peer Review

## Introduction

Meconium ileus (MI) is characterised by neonatal intestinal obstruction caused by the accumulation of desiccated and inspissated intraluminal meconium[1]. Around 15% of patients with pancreatic insufficient cystic fibrosis (CF) present with MI [2] but MI is also recorded rarely in normals and pancreatic sufficient CF [3]. It is a matter of debate as to what extent long-term outcome in CF is affected by MI.

Two groups from areas where new born screening (NBS) is established have suggested that patients presenting with MI have a worse prognosis in terms of lung function than those without MI diagnosed through NBS. [4,5,6,7] One of these groups, the Wisconsin group [5,6,7] also found MI patients had poorer growth.

However, 3 studies have suggested that MI patients have the same prognosis as patients presenting with other symptoms, not diagnosed through new-born-screening. Munck et al [8] in 2006 compared 26 children presenting with MI diagnosed with CF at a median age of 1 month to 26 children without MI presenting with other symptoms (unscreened) diagnosed with CF at a median age of 3.5 months. They compared height and weight z scores at 1, 3, 6, 10 and 15 years of age. They also compared forced vital capacity (FVC) and first second forced expired volume (FEV1) at 6, 10 and 15 years. There was no difference between the two groups in growth or lung function and they concluded that presenting with MI made no difference to clinical outcome compared to presenting with other symptoms.

The second study [9] compared 158 patients presenting with MI to 1175 CF patients presenting with other symptoms again in a pre-new born screening era. They compared 2 subgroups based on date of birth and showed that MI patients born between 1963 and 1972 had lower weight and height percentiles at age 13 years compared to non-MI patients. However, subjects born between 1973 and 1982 showed no difference in height and weight at 13 years. There were also no differences in FVC, FEV1, or forced expiratory flow at 25% to 75% of FVC (FEF<sub>25-75</sub>) in this subgroup. There was a significantly better survival in the later compared to the earlier cohort, particularly in the MI group in

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3 the first year of life. This study suggests that advances in medical care especially in the perinatal period  
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5 improved the prognosis of patients in the MI group.  
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9 The merits of the study by Kerem et al [9] include the large sample size and long time period of the  
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11 study. However, the problem with such a long time period is the changes in medical practice taking  
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13 place in this time. Although the authors tried to limit these differences by analysing the results in 2  
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15 cohorts, this resulted in a lack of pulmonary function test data to power the study.  
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19 The most recent study [10] retrospectively compared 60 CF subjects with a history of MI (mean age of  
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21 diagnosis 0.4 months) to 310 without MI presenting with other symptoms (mean age of diagnosis 21.8  
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23 months). Using a combination of cross-sectional and longitudinal analyses, they showed that there was  
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25 no difference in lung function between the 2 groups. Although this study is more recent, the large age  
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27 range of the study subjects (0-48 years) means that it is highly likely that there was wide variation over  
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29 time in the medical care that the patients received.  
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33 The aim of our single centre study is to test the hypothesis that with current standards of medical care  
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35 and in an era of non-NBS there is no difference in clinical outcome between CF patients presenting  
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37 with MI and patients without MI presenting with other symptoms.  
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41 The question has important practical as well as theoretical implications. If patients presenting with MI  
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43 have the same or better prognosis than those diagnosed later with other symptoms, despite in many  
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45 cases having had to undergo a major abdominal operation, this would be a pointer to the benefits of  
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47 early diagnosis of CF, which has been disputed by some [11]. On the other hand, if they do worse,  
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49 despite modern treatment, this implies that new treatment strategies are needed in this group and that  
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51 they would have potentially more to gain from novel, disease-modifying therapies.  
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## Material and Methods

### Study Subjects:

CF patient data is updated on the Royal Brompton Hospital CF database after the patients' annual review by the CF nurse or secretary. By the 1<sup>st</sup> January 2008, 665 subjects had been registered onto the database since it began in 1986. All had a diagnosis of CF confirmed with a positive sweat test (a chloride value >60mmol/l in two sweat samples) and/or had the presence of two recognised CF disease-causing genetic mutations. Of the 665 subjects 75 of these had presented with meconium ileus and 590 with non meconium ileus (non-MI) symptoms including respiratory symptoms and/or failure to thrive. To be included, subjects had to be at least 15 years old at the time of the study (i.e. born before 1<sup>st</sup> January 1993). Subjects had to have a minimum of 5 recorded annual pulmonary function tests in terms of percent predicted first second forced expired volume (FEV1%pr) and percent predicted forced vital capacity (FVC%pr) from the age of 8 years. They were also required to have at least 5 recordings of annual height and weight z-scores (HtZ and WtZ respectively) from the age of 2 years. Pulmonary and anthropometric data was analysed up to and including the 15<sup>th</sup> year of life. Ethical approval was obtained from the Royal Brompton Hospital Research Ethics Committee. From 16 years of age many of the subjects were referred to other adult CF tertiary centres so survival data was the only outcome measure recorded thereafter. These were obtained by telephone contact to the adult tertiary centres to which the children had been referred.

### Study Design:

The primary objective of our study was to test the hypothesis that, in an era of non-NBS there is no difference in clinical outcome between CF patients presenting with MI (MI group) and those without MI presenting with other symptoms (non-MI group). We used a retrospective longitudinal study to compare growth and pulmonary function data of eligible subjects in MI and non-MI groups on a year-by-year basis. Details of treatment protocols can be found at

<http://www.rbht.nhs.uk/healthprofessionals/clinical-depts/paediatrics/childrencf/>

### Methods/Statistical Analysis:

The primary outcomes were annual HtZ /WtZ scores (age 2-15 years) and FVC%pr/ FEV1%pr (age 8-15 years). 8 years was taken as the age at which pulmonary function testing could be accurately



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3 reproduced. Pulmonary function was measured using a Jaeger CompactLab pneumotachograph in the  
4 lung function laboratory by trained technicians. FEV<sub>1</sub> and FVC were measured and expressed as  
5 percentages of predicted values obtained from equations based on gender and height by Rosenthal et al  
6 [12]. Weight (minimal underclothing) and height (Harpenden stadiometer) were measured and  
7 expressed as standard deviation scores (Z-scores) using published population means and standard  
8 deviations [13]. Baseline characteristics of the study groups were compared using Chi Squared  
9 analysis with Fisher's exact test for categorical data and Mann-Whitney for continuous data.  
10 Characteristics included sex and age, genotype ( $\Delta F508/\Delta F508$  homozygosity), use of pancreatic  
11 enzymes and presence of chronic *Pseudomonas aeruginosa* in lung secretions (defined as 2 or more  
12 isolations of *Pseudomonas aeruginosa* necessitating the use of long term anti-*Pseudomonas* nebulised  
13 antibiotic inhaled therapy).  
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27 It was calculated [14,15] that in order to detect a mean difference in FEV<sub>1</sub>%pr of 10% between MI and  
28 non-MI groups, a sample size of at least 20 subjects (with each subject having 5 measurements over at  
29 least 5 years i.e. 100 observations) is needed for a 5% significance level at 80% power.  
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35 A random selection of subjects was made from the non-MI group for matched selection purposes by  
36 employing the Excel RAND function to provide approximately a 2:1 non-MI:MI ratio.  
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41 Primary outcomes were analysed using mixed effects regression models REML (restricted maximum  
42 likelihood method). The MI and non-MI groups were compared for each of the main outcomes:  
43 FEV<sub>1</sub>%pr, FVC%pr, HtZ and WtZ over time. The models were adjusted for sex, genotype, age of  
44 diagnosis, pancreatic status and chronic *Pseudomonas aeruginosa* pulmonary status. The statistical  
45 software package STATA version 10.1 was used. Survival in the two groups was compared using  
46 Kaplan-Meier analysis. Graphic representation of the outcomes of lung function and growth was done  
47 using MS Excel with the error bars representing the 5<sup>th</sup> and 95<sup>th</sup> percentiles around median values for  
48 MI and non-MI groups. Subgroup comparison of FEV<sub>1</sub>%pr at the age of 10 years was analysed using  
49 Mann Whitney (SPSS version 12).  
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## Results

From the original 75MI and 590 non-MI subjects registered on the CF database, 38/75 MI subjects were born before 1<sup>st</sup> January 1993 and had sufficient pulmonary function and anthropometric data (median age of diagnosis 1 day) to meet the above criteria. Of these 38, thirty underwent a newborn surgical procedure (14 had intestinal resection), 7 subjects were successfully treated with gastrograffin enemas and 1 passed a meconium plug spontaneously at 19 hours of age. 283/ 590 non-MI subjects met the inclusion criteria. From this population of 283, seventy-six subjects were selected at random to act as controls for the MI population (median age of diagnosis 7 months). 30 of these presented with a history of combined chest problems and failure to thrive, 16 with chest problems alone, 15 failure to thrive alone and 15 with other modes.

The Royal Brompton Hospital CF database contained up to date data for all included subjects. The database is complete in that as far as we are aware, if a patient has been seen in the annual clinic, the data is registered on the database. However, not all included patients had data recorded from each annual review. From the 8-year review onwards, on average lung function data for 86% non-MI and 81% MI patients was recorded annually. From 2 to 8 years, at each review on average only 60% non-MI and 56% MI patients had anthropometric measurements recorded. We believe that missing data is largely due to late referral to the Brompton Hospital and non-attendance at annual appointments.

Since the age of 15, five subjects from the non-MI group have subsequently died compared to none from the MI group (by 1<sup>st</sup> January 2009). This difference was not statistically different. (See figure 1).

There was no significant difference between MI and non-MI groups in terms of genotype, sex, median date of birth and median age of first attendance at annual review clinic (table 1). There was also no difference in chronic *Pseudomonas* colonisation (defined as 2 or more previous sputum isolations of *Pseudomonas aeruginosa* and on long term nebulised anti-*Pseudomonas* antibiotics) or in the median age of first sputum isolation of *Pseudomonas aeruginosa*. There was no significant difference in pancreatic enzyme use. We did not make pancreatic sufficiency an exclusion criteria because, although rare, patients who are pancreatic sufficient can get MI. In order to reflect the CF population, the 6 pancreatic sufficient non-MI patients were therefore included. There was a significant difference,

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3 however, in the median age of commencing pancreatic enzymes (1 day old in the MI group versus 211  
4 days old in the non-MI group,  $p=0.00$ ).  
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10 Figures 2 to 5 display graphically how the median values of all 4 primary outcomes vary over time for  
11 both MI and non-MI groups. Figure 2 shows a decline over time for both groups in median FEV1%pr  
12 but the median values are higher in the MI group at all but 1 time point (8 years). Figure 3 shows the  
13 decline over time of median FVC%pr in both groups over the study period but with values higher in the  
14 MI group at all time points. Figure 4 shows the median HtZ score decreasing over the time period of  
15 the study in both groups. Again, the median values are higher at all time points in the MI group apart  
16 from 1 (10 years). Figure 5 shows higher median values for WtZ score at all but 2 time points in the MI  
17 group (6 and 12 years), however the overall linear trend is for the median WtZ to decrease in the MI  
18 group but increase in the non-MI group over time.  
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31 Table 2 shows a statistical comparison of MI and non-MI groups for all 4 outcomes over the time  
32 period of the study. The mixed effects REML regression model, adjusting for sex, age of diagnosis,  
33 genotype, pancreatic status and presence of chronic Pseudomonas aeruginosa infection and age of  
34 diagnosis showed no statistically significant difference between the 2 groups for all 4 parameters over  
35 the time period of the study. There was a non-statistically significant trend for the FEV1%pr to be  
36 higher on average by 3.36% per year in the MI group compared to the non-MI group. Similar trends  
37 were seen for the other outcome measures (2.87% per year for FVC%pr, 0.06 HtZ per year and 0.01  
38 WtZ per year in favour of the MI group).  
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There is a possibility that over the time course of the study prognosis and survival has improved which  
could influence the results. We therefore compared the FEV1%pr at the age of 10 years between MI  
and non-MI subjects in 2 subgroups, those born < 01/01/1989 and those born between 02/01/1989 and  
01/01/1993. In the earlier subgroup, at the age of 10 years, FEV1 was recorded for 27/33 non-MI  
subjects with a median FEV1%pr of 83%. This was compared to 13/16 MI subjects with a median  
FEV1%pr of 96%. This difference, however, was not statistically significant ( $p=0.260$ , Mann  
Whitney). In the later subgroup, at the age of 10 years, 43/43 non-MI subjects had a median FEV1%pr

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3 of 89%. This compared to 94% in MI subjects (n=20/22). This difference again was not significant  
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5 (p=0.114, Mann Whitney).  
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## Discussion

Here, we report that during the first 15 years of life there was no statistically significant difference in lung function and growth outcomes between children presenting with meconium ileus and those presenting later with other symptoms during an era of non-NBS. There was a non-significant trend for the prognosis of the MI group to be slightly better than the non-MI group in terms of growth and lung function. This is despite the fact that many of the meconium ileus group had an invasive procedure in the newborn period, which is likely to predispose to acquisition of *Pseudomonas aeruginosa*. [16], (Our results did not demonstrate this however with MI subjects having the same timing of first *Pseudomonas* colonisation and rate of chronic infection as non-MI subjects). The significant difference in the median age of starting pancreatic enzymes (1 day MI versus 211 days non-MI) is most likely a direct result of earlier diagnosis.

There were more deaths in the non-MI group compared to the MI group though this difference was not statistically significant.

The strengths of this study include the longitudinal design, and the fact that anthropometric, lung function measurements and CF treatment after the correction of MI was standardised in a single centre. The main weakness is the study size. The inclusion criteria ensured sufficient longitudinal data to power the study but also meant that the final sample excluded patients with fewer data points. Longer follow-up would have been more ideal but this was difficult due to referral of many patients to other adult tertiary centres. However the fact that up to 15 years after surgery (in the MI group) we could not detect a difference between the two groups in the major prognostic factors (spirometry, nutrition) is reassuring,

There is also the possibility, however, that over the 15-year time course of the study prognosis and survival has improved which could influence the results. However, when 2 subgroups were analysed separately based on year of birth (<01/01/89 or 02/01/89-01/01/93) there was no significant difference in FEV1%pr at age 10 years between MI and non-MI subjects. However, drawing any conclusions from this is difficult due to the small numbers compared.

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5 An alternative study design would be to use a large national database, which would enable larger  
6 numbers to be studied. This approach is not without problems; treatment protocols vary from centre to  
7 centre, and for most if not all databases, there is no attempt to quality control the anthropometric and of  
8 particular importance, the lung function measurements. In a single centre study such as ours there is  
9 careful calibration of equipment and standardisation of measurement techniques.  
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18 Our findings support our original hypothesis that with current standards of medical care and in an era  
19 of non-new born screening, there is no difference in clinical outcome between CF patients presenting  
20 with MI and patients without MI presenting with other symptoms.  
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26 Our conclusion correlates with that of the study by Munck et al detailed earlier who also compared, on  
27 a smaller scale, MI presenting patients to a non-screened population presenting with other symptoms.  
28 [8]. It also agrees with the findings of Kappler et al [10], who, over a variable study period, showed no  
29 difference in lung function between MI and non-MI non-screened subjects, both on longitudinal and  
30 cross-sectional analyses and no difference in nutritional parameters on cross-sectional analysis. Our  
31 results also correlate with the 2<sup>nd</sup> cohort of patients (diagnosed between 1973 and 1982) in the study by  
32 Kerem et al in which there was no significant difference between MI and non-MI non-screened groups  
33 in terms of lung function and growth.  
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43 Our results disagree with those studies comparing MI presenting patients to those without MI  
44 diagnosed by new born screening [4,5,6,7]. These studies have all shown a worse outcome for MI as  
45 compared to non-MI NBS patients. The Wisconsin CF Neonatal Screening Project prospectively  
46 compared 32 MI to 50 non-MI patients diagnosed by NBS from diagnosis to twelve years of age [5,  
47 6,7]. They showed that MI patients had significantly worse lung function as well as growth over the  
48 study period. Evans et al [4] compared 39 MI with 39 non-MI NBS patients at just one time point.  
49 They showed no difference in growth between the two groups but the MI group had significantly worse  
50 FEV1%pr. These studies would suggest that, in these centres at least, either MI per se, or more likely,  
51 the effects of interventions in the newborn period, carry a long-term adverse effect.  
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3 It is recognised by some [17, 18, 19, 20] but not by others [21, 22] that earlier diagnosis is beneficial to  
4 long term clinical outcome in CF. The likely explanation for our findings differing from findings in  
5 studies using NBS patients as a control group [4, 5, 6, 7] is that although many of our MI subjects  
6 required surgery, the earlier diagnosis of the MI group compared to the non-MI group allowed earlier  
7 institution of CF therapy. This may have offset any possible disadvantage to the MI group of invasive  
8 interventions in the newborn period. This delay in diagnosis is not as apparent when comparing MI-  
9 presenting patients to non-MI patients diagnosed soon after birth by NBS.  
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19 In summary, we have shown that within a non-screened population CF patients presenting with MI  
20 have the same prognosis (up until the age of 15 years) as those presenting later with other symptoms.  
21 Comparing our results to studies involving non-MI NBS subjects as controls, lends support to the  
22 benefits of early diagnosis and, indirectly, NBS. Future studies should focus on the outcomes of MI  
23 patients compared with non-MI patients diagnosed through NBS, to determine if presenting with MI  
24 truly affects long-term outcome in CF in the modern era of surgery and intensive care. If this is the  
25 case, there will be a need to focus on improving the peri-operative care of these patients.  
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For Peer Review

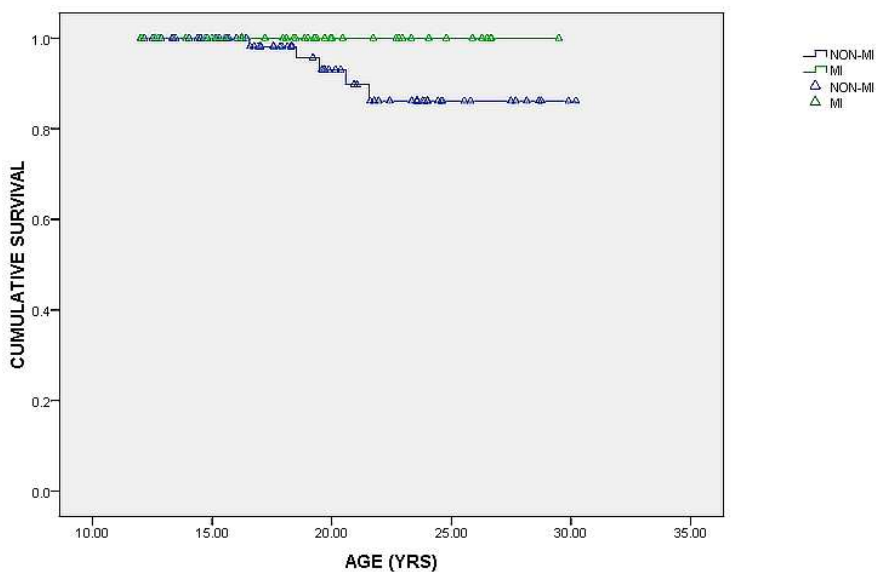


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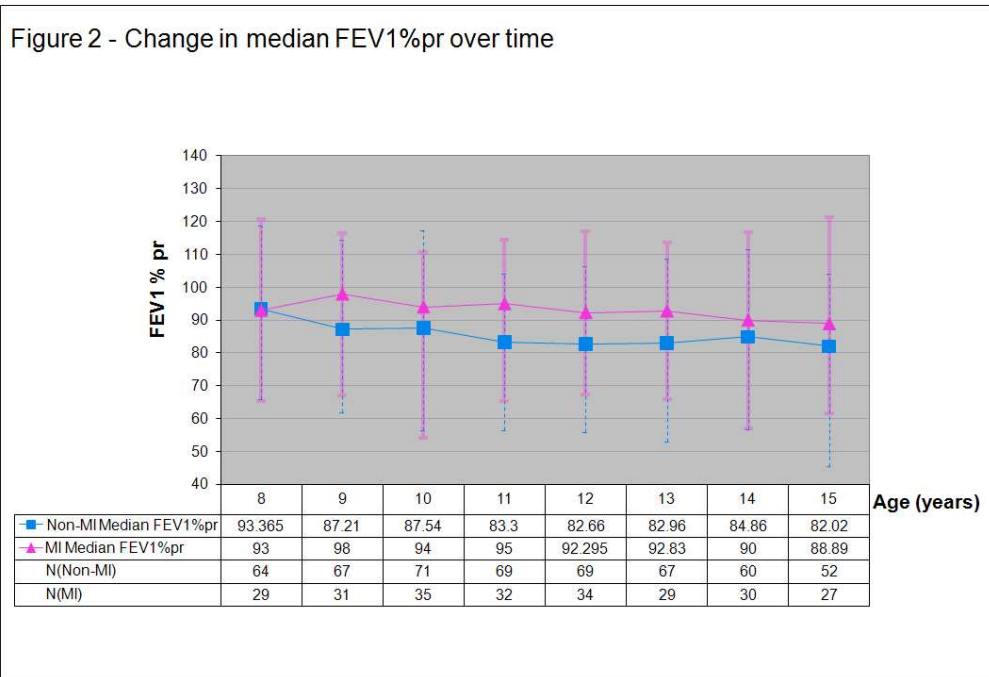
Kaplan-Meier cumulative survival for MI and Non-MI group. Censored subjects either still alive or died from non CF cause.  
218x134mm (96 x 96 DPI)

Review

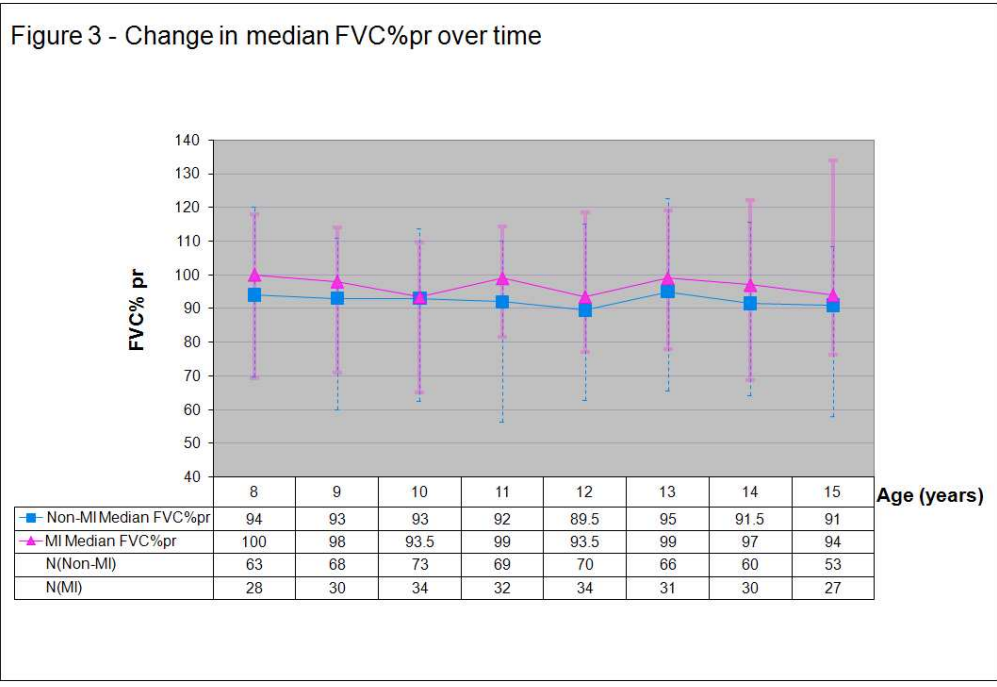
**Table 1** Subject Characteristics

Characteristic		MI (n=38)	Non-MI(n=76)	P value
<b>Genotype</b>	<b>ΔF508/ΔF508</b>	25	43	0.53
	<b>Others</b>	12 (one missing)	29 (4 missing)	
<b>Chronic Pseudomonas infection<sup>a</sup></b>	<b>Yes</b>	18	37	1.00
	<b>No</b>	20	39	
<b>Median age of first Pseudomonas colonisation<sup>b</sup></b>		5.1	5.0	0.265
<b>Pancreatic enzyme use</b>	<b>Yes</b>	38	70	0.10
	<b>No</b>	0	6	
<b>Median age commenced pancreatic enzymes (years)</b>		0.003	0.58	0.00
<b>Sex</b>	<b>Male</b>	16	31	1.0
	<b>Female</b>	22	45	
<b>Median date of birth</b>		22/09/1989	05/06/1989	0.93
<b>Median age at diagnosis (months)</b>		0.0329	7.44	0.00
<b>Median age of first attendance<sup>c</sup></b>		2.02	2.87	0.35

<sup>a</sup>Defined as 2 or more previous sputum isolations of *Pseudomonas aeruginosa* and on long term nebulised anti-Pseudomonas antibiotics; <sup>b</sup>Defined as median age of first sputum isolation of *Pseudomonas aeruginosa*; <sup>c</sup>Median age of first attendance at annual review clinic; MI: subjects presenting with meconium ileus; non-MI: subjects without meconium ileus presenting with other symptoms; n: number of subjects.



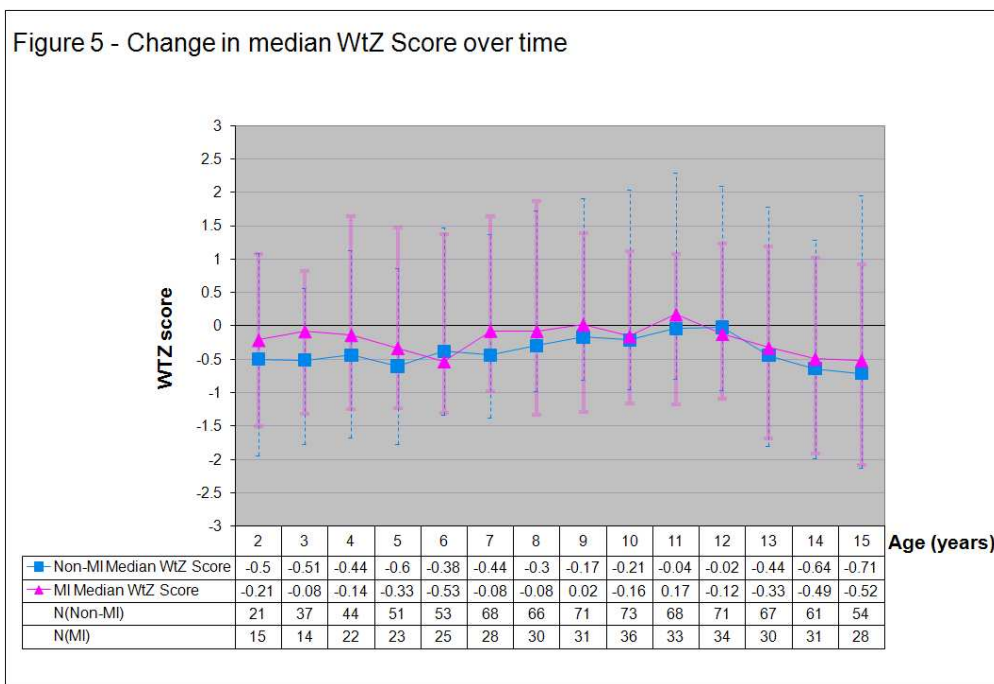
Change in median FEV1%pr over time in MI versus non-MI groups. Error bars represent 5th and 95th percentiles for MI and non-MI group median values. FEV1%pr: percent predicted forced expiratory volume in 1 second; N: number of subjects; MI: subjects presenting with meconium ileus; non-MI: subjects without meconium ileus presenting with other symptoms.



Change in median FVC%pr over time in MI versus non-MI groups. Error bars represent 5th and 95th percentiles for MI and non-MI group median values. FVC%pr: percent predicted forced vital capacity; N: number of subjects; MI: subjects presenting with meconium ileus; non-MI: subjects without meconium ileus presenting with other symptoms.



Change in median HtZ score over time in MI versus non-MI groups. Error bars represent 5th and 95th percentiles for MI and non-MI group median values. HtZ score: Standard deviation score of height from median; N: number of subjects; MI: subjects presenting with meconium ileus; non-MI: subjects without meconium ileus presenting with other symptoms.



Change in median WtZ score over time in MI versus non-MI groups. Error bars represent 5th and 95th percentiles for MI and non-MI group median values. WtZ score: standard deviation score of weight from median; N: number of subjects; MI: subjects presenting with meconium ileus; non-MI: subjects without meconium ileus presenting with other symptoms.



**TABLE 2** Mixed effects REML regression model—coefficients for MI versus non-MI subjects

	<b>Coefficient</b>	<b>P value</b>	<b>95% CI</b>
<b>FEV1%pr</b>	3.36	0.11	-0.71 to 7.42
<b>FVC%pr</b>	2.87	0.13	-0.81 to 6.54
<b>HtZ</b>	0.06	0.80	-0.39 to 1.20
<b>WtZ</b>	0.01	0.96	-0.35 to 0.38

MI: subjects presenting with meconium ileus; non-MI: subjects without meconium ileus presenting with other symptoms; FEV1%pr: percent predicted first second forced expired volume; FVC%pr: percent predicted forced vital capacity; HtZ: Height z-score; WtZ: Weight z-score