

Online Data Supplement

Title: Structural determinants of long term functional outcomes in young children with cystic fibrosis

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AREST CF Study population

All children diagnosed with CF in Western Australia are managed at the Princess Margaret Hospital for Children (PMH), Perth and children diagnosed in Victoria who are managed at the Royal Children's Hospital (RCH), Melbourne. Over 95% of eligible children enrolled into the Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST CF) program. In Australia, the diagnosis of CF is made in the majority of infants by six weeks of age, following detection by newborn screening [1]. The majority of infants have no respiratory symptoms at diagnosis but may have pulmonary inflammation and infection [2]. The AREST CF early surveillance program includes a comprehensive assessment soon after diagnosis (approximately at three months of age) and then annually until six years of age. Since 2005 a chest CT under general anesthesia was also included in the bi-annual follow-up in children up to the age of 5 years in Melbourne and in the annual follow-up to the age of 6 years in Perth [2]. The study was approved by the ethics committee of the 2 participating institutions and parents of all patients gave informed consent.

Computed tomography

Chest CTs were performed under general anesthesia. Children were intubated with a cuffed tracheal tube and a standardised recruitment manoeuvre was used to reduce procedure related atelectasis. A volume controlled, volumetric (since 2007) or limited slice (prior to 2007) chest CT scan was obtained at end inspiration (Prs = 25cm H₂O) and end expiration (Prs = 0cm H₂O) as described previously [3]. CT images were scored for the presence of structural lung disease using a simplified Brody CF-CT scoring method [2, 3]. Each scan was examined in six lobes for volumetric scans (with the lingual treated as a separate lobe), and six zones for limited slice scans (upper, middle and lower areas of the left and right lungs). For each abnormality separately, a score was given per lobe/zone of zero (none present), one (present in less than half of the lobe/zone), or two (present in at least half of the lobe/zone). Lobe/zone scores were summed, and thus for each abnormality there was a maximum score of 12. The following structural abnormalities were scored on inspiration scans: bronchiectasis (bronchus-artery diameter ratio > 1, or lack of tapering for in-plane bronchi), mucous plugging (high-density occlusion of an airway or tree-in-bud sign), and bronchial wall thickening (assessed subjectively by considering the width and brightness of airway walls). The total CT score was determined by summing these three sub-scores, and thus has a maximum score of 36. Trapped air (geographic hypodense regions) was assessed on expiration scans. Details of the scanners and settings used have been previously published [4].

Spirometry

Spirometry measurements performed during admissions or outpatient visits for AREST CF cohort were obtained retrospectively, from PMH and RCH patient

records for all children until the age of 6, for subgroup of children with consent to use patient files up to later ages. Secondly, data linkage with ACDFR was used to obtain additional measurements for all children aged 6 years and older with data available in the ACDFR. Spirometry was performed according to current ATS/ERS guidelines [5, 6]. For the years where more than one measurement was available per child, the annual best was the only one included in analysis.

References

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eTable 1. Absolute Broody Cf-CT scores at ages 5 to 6 years

	<i>Bronchiectasis</i>	<i>Bronchial wall thickening</i>	<i>Trapped air</i>	<i>Mucus plugging</i>	<i>Total CT score</i>
<i>Absolute scores</i>	<i>3 (1-7)</i>	<i>9 (6-11)</i>	<i>1 (3-6)</i>	<i>0 (0-1)</i>	<i>9 (16-25)</i>
<i>Median (IQR)</i>					

eTable 2. Sensitivity analysis for structural predictors of FEV₁ Z score decline**a) Children than only had 1 follow-up spirometry measurement were excluded from analysis**

CF-CT extent score at age 5-6 years	Mean change (95% CI) p-value (unadjusted) n=686	Mean change (95% CI) p-value (adjusted*) n=650
Mucus plugging	-0.21 (-0.31, -0.11) p<0.001	-0.18 (-0.27, -0.09) p<0.001
Trapped air	-0.11 (-0.16, -0.05) p<0.001	-0.09 (-0.14, -0.04) p=0.001
Bronchiectasis	-0.05 (-0.09, -0.01) p=0.027	-0.03 (-0.07, 0.01) p=0.203
Bronchial wall thickening	-0.02 (-0.07, 0.03) p=0.529	-0.01 (-0.06, 0.03) p=0.626
Total score	-0.03 (-0.05, -0.01) p=0.002	-0.02 (-0.04, -0.00) p=0.014

b) Children than only had 2 follow-up spirometry measurements were excluded from analysis

CF-CT extent score at age 5-6 years	Mean change (95% CI) p-value (unadjusted) n=614	Mean change (95% CI) p-value (adjusted*) n=584
Mucus plugging	-0.23 (-0.33, -0.13) p<0.001	-0.22 (-0.31, -0.12) p<0.001
Trapped air	-0.12 (-0.18, -0.06) p<0.001	-0.11 (-0.17, -0.06) p<0.001
Bronchiectasis	-0.05 (-0.09, -0.00) p=0.046	-0.04 (-0.08, 0.01) p=0.117
Bronchial wall thickening	-0.03 (-0.08, 0.03) p=0.330	-0.02 (-0.07, 0.04) p=0.537
Total score	-0.03 (-0.05, -0.01) p=0.001	-0.03 (-0.05, -0.01) p=0.004

* Models were adjusted for: intrinsic disease severity (Homozygous D508 mutation, pancreatic sufficiency and gender), test centre and age at spirometry.

eTable 3. Structural predictors of FVC Z score decline based on a CT scan available at ages 5-6 years and annual spirometry measurements in the following 10 years.

ZFVC	Unadjusted β (95% CI) n=697	Adjusted β (95% CI) n=683
Mucus plugging	-0.17 (-0.26, -0.09) p<0.001	-0.15 (-0.23, -0.07) p<0.001
Trapped air	-0.08 (-0.13, -0.03) p=0.001	-0.06 (-0.11, -0.02) p=0.007
Bronchiectasis	-0.04 (-0.07, 0.00) p=0.050	-0.03 (-0.06, 0.01) p=0.167
Bronchial wall thickening	-0.01 (-0.05, 0.04) p=0.755	-0.00 (-0.04, 0.04) p=0.918
Total CT score	-0.02 (-0.04, -0.01) p=0.008	-0.02 (-0.03, -0.00) p=0.044

eTable 4. Structural predictors of FEV_{FVC} Z score decline based on a CT scan available at ages 5-6 years and annual spirometry measurements in the following 10 years.

ZFEV _{FVC}	Unadjusted β (95% CI) n=697	Adjusted β (95% CI) n=688
Mucus plugging	-0.07 (-0.14, -0.01) p=0.035	-0.06 (-0.13, 0.00) p=0.061
Trapped air	-0.04 (-0.07, 0.00) p=0.055	-0.03 (-0.07, 0.00) p=0.125
Bronchiectasis	-0.02 (-0.05, 0.01) p=0.205	-0.01 (-0.04, 0.02) p=0.559
Bronchial wall thickening	-0.03 (-0.06, 0.01) p=0.127	-0.03 (-0.06, 0.01) p=0.129
Total CT score	-0.01 (-0.02, -0.00) p=0.029	-0.01 (-0.02, 0.00) p=0.083

eTable 5. Structural predictors of ZFEF₂₅₇₅ Z score decline based on a CT scan available at ages 5-6 years and annual spirometry measurements in the following 10 years.

ZFEF ₂₅₇₅	Unadjusted β (95% CI) n=696	Adjusted β (95% CI) n=685
Mucus plugging	-0.13 (-0.23, -0.04) p=0.004	-0.11 (-0.20, -0.03) p=0.011
Trapped air	-0.07 (-0.12, -0.01) p=0.011	-0.05 (-0.10, -0.00) p=0.043
Bronchiectasis	-0.02 (-0.06, 0.02) p=0.227	-0.01 (-0.05, 0.03) p=0.750
Bronchial wall thickening	-0.01 (-0.06, 0.03) p= 0.544	-0.01 (-0.06, 0.03) p=0.621
Total CT score	-0.02 (-0.03, -0.00) p=0.043	-0.01 (-0.03, 0.01) p=0.189

eTable 6. Structural predictors of WHO BMI for age Z score decline based on a CT scan available at ages 5-6 years and annual spirometry measurements in the following 10 years.

BMI for age Z score	Unadjusted β (95% CI) n=695	Adjusted β (95% CI) n=686
Mucus plugging	-0.11 (-0.19, -0.03) p=0.007	-0.10 (-0.18, -0.02) p=0.017
Trapped air	-0.05 (-0.10, -0.01) p=0.024	-0.04 (-0.08, 0.01) p=0.118
Bronchiectasis	-0.05 (-0.08, -0.01) p=0.007	-0.04 (-0.08, -0.02) p=0.022
Bronchial wall thickening	-0.04 (-0.08, 0.02) p= 0.061	-0.03 (-0.08, 0.01) p=0.094
Total CT score	-0.02 (-0.04, -0.01) p=0.004	-0.02 (-0.03, -0.00) p=0.017

eTable 7. Adjusted rate of FEV₁ Z score decline per year in presence/absence of different structural abnormality groups.

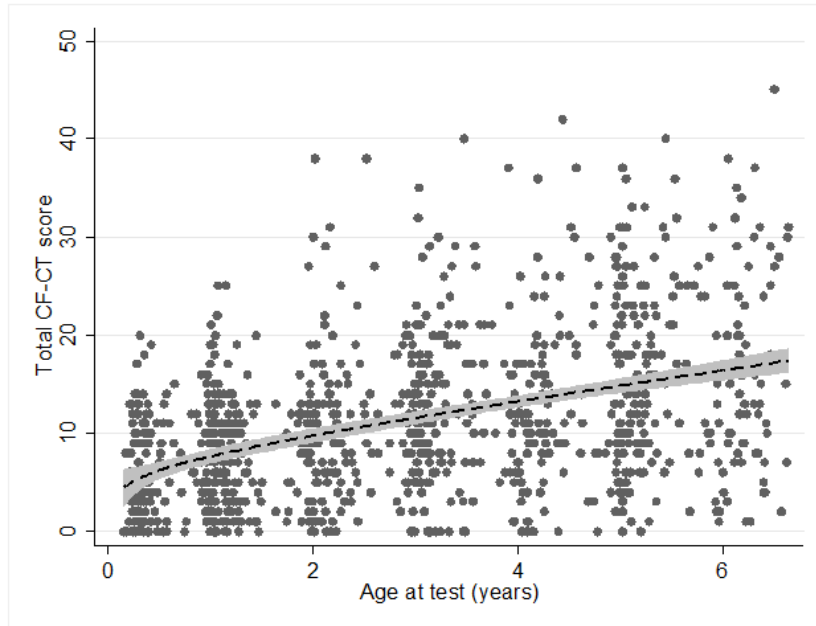
CF-CT presence at age 5-6 years	Abnormality absent Rate of decline per year (95% CI) p-value	Abnormality present Rate of decline per year (95% CI) p-value
Mucus plugging	-0.00 (-0.07, 0.06) p=0.903	-0.08 (-0.14, -0.01) p=0.017
Trapped air	-0.03 (-0.11, 0.05) p=0.486	-0.07 (-0.11, -0.02) p=0.004
Bronchiectasis	-0.08 (-0.14, -0.02) p=0.011	-0.05 (-0.10, -0.00) p=0.037
Bronchial wall thickening	-0.14 (-0.26, -0.03) p=0.014	-0.06 (-0.10, -0.02) p=0.001

eTable 8. Sensitivity analysis for modelling CF-CT score as continuous variable: hazard ratios of time until FEV₁ Z score falls below -1.64 for every 1 point increase in a total CF-CT score

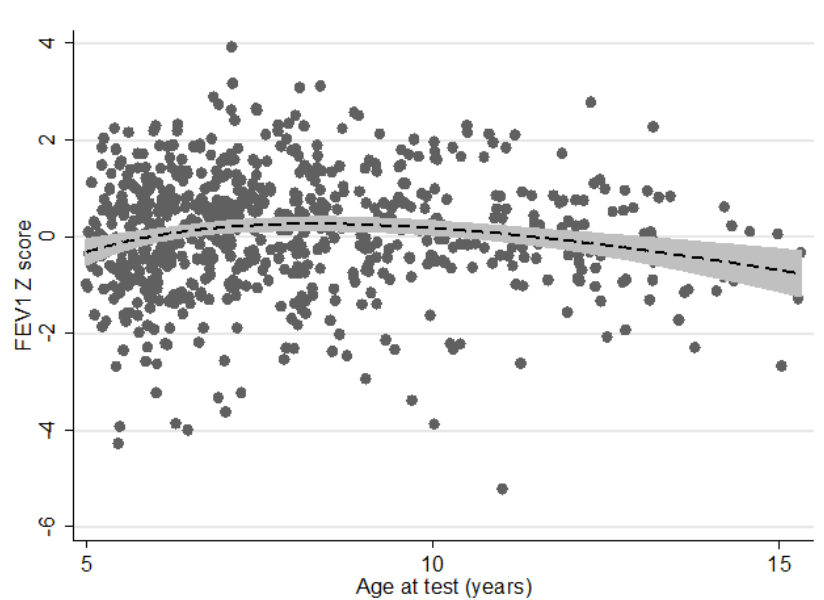
Age (years)	Hazard ratio (unadjusted) (95% CI) p-value	Hazard ratio (adjusted) (95% CI) p-value
1-2	1.00 (0.84, 1.07) p=0.993	1.01 (0.94, 1.08) p=0.876
3-4	1.04 (0.99, 1.08) p=0.089	1.04 (0.99, 1.09) p=0.093
5-6	1.06 (1.02, 1.10) p=0.002	1.06 (1.02, 1.11) p=0.007

eFigure 1. (a) Progression of structural lung disease as measured by a total CF-CT score in AREST CF cohort (b) Decline of FEV₁ through adolescence using linked data (c) Decline of WHO BMI for age Z score through adolescence using linked data.

a)



b)



c)

