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

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

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Take-home message: Structural lung changes identified on a chest CT scan in children with cystic fibrosis under 6 years of age can identify those at risk of adverse long-term outcomes.

Tables and figures

Abstract

Background: Accelerated lung function decline in individuals with cystic fibrosis (CF) starts in adolescence with respiratory complications being the most common cause of death in later life. Factors contributing to lung function decline are not well understood, in particular its relationship with structural lung disease in early childhood. Detection and management of structural lung disease could be an important step in improving outcomes in CF patients.

Methods: Annual chest computed tomography (CT) scans were available from 2005 to 2016 as a part of AREST CF cohort for children aged 3-months to 6-years. Annual spirometry measurements were available for 89.77% of the cohort (n=167 children at age 5-6 years) from ages 5 to 15 years through outpatient clinics at Perth Children's Hospital and The Royal Children's Hospital in Melbourne. (n=697 measurements, age 9.3 (2.1) years).

Findings: Children with a total CT score at 5-6 years above the median were more likely to have abnormal FEV_1 (aHR 2.67 (1.06, 6.72) p=0.037) during the next 10 years compared to those below the median chest CT score. The extent of all structural abnormalities except bronchial wall thickening were associated with lower FEV_1 Z scores. Mucus plugging and trapped air were the most predictive sub-score (adjusted mean change -0.17 (-0.26, -0.07) p<0.001 and -0.09 (-0.14, -0.04) p<0.001 respectively).

Interpretation: Chest CT identifies children at an early age who have adverse long-term outcomes. The prevention of structural lung damage should be a goal of early intervention and can be usefully assessed with chest CT. In an era of therapeutics that might alter disease trajectories, chest CT could provide an early readout of likely long-term success.

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Introduction

Cystic fibrosis (CF) is the most common life-shortening autosomal recessive disease affecting children, with an estimated incidence of 1 in 2500 live births in Caucasian populations [1]. Spirometry, an objective measure of lung function, is the most universally performed and accepted clinical test by which a patient's respiratory status, progress or decline is assessed. Forced expiratory volume in 1 second (FEV_1) is the key clinical efficacy measure and driver in the definition of disease stage, treatment decisions, as an U.S. Food and Drug Administration (FDA) approved primary outcome measure for clinical trials and in the regulatory approval of respiratory therapies in CF [2, 3].

Spirometry is usually not performed in children under 6 years of age with CF and it commonly remains within the range of values in healthy children from 6 years old until early adolescence, limiting its usefulness for assessing both clinical status and effects of interventions in early childhood. Hence, there is a great need for a biomarker that can be easily measured in early life and that can predict longer term outcomes.

Australian and international CF registries usually report spirometry data as "annual best" from the age of 6 years [4-6]. These data have shown that median percent predicted FEV_1 increases in successive cohorts. However, when assessing FEV_1 population trajectories, cohorts with a lower median FEV_1 at age 6, tend to maintain lower FEV_1 throughout life with little change in the rate of the decline. This highlights that early childhood represents an important developmental period when intervention strategies could potentially prevent the early onset of lung damage and thereby have

beneficial long term effects for patients with CF. Standard spirometry fails to detect changes in structural lung disease [7]. Moreover, improvement in early lung function in successive cohorts has not prevented the significant decline that remains evident, commencing during adolescence in CF [6, 8].

There is strong evidence that structural lung disease in CF begins in infancy, is progressive and is associated with inflammation and infection [9-11], frequency of pulmonary exacerbations and reduced quality of life [12, 13]. Chest computed tomography (CT) is considered the “gold standard” for demonstrating CF structural lung disease.

One of the challenges in using chest CT for assessing clinical status, or as a potential surrogate endpoint in early intervention trials, is trying to assess its relationship with traditional outcomes and anticipating what long term effects might be expected from an intervention in early life when lung damage is relatively mild. The majority of published work has typically focused on comparisons tracking disease progression using spirometry and CT in school-aged or older children and adults [7, 14-16]. The relations between the commonly observed CT-defined structural lung abnormalities in young children and long term functional outcomes are not known.

Data were available from the Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST CF) longitudinal pediatric cohort and routine outpatient clinic visits. We aimed to assess whether structural lung abnormalities in early childhood are predictive of lung function decline in the following 10 years of life and if so, to

determine what the optimal age is to perform a CT scan in young children. These issues are of significant clinical importance since solutions would allow for closer clinical monitoring of high risk young children and provision of an informative surrogate to monitor the effects and aid the development of interventions to prevent structural disease and consequent FEV_1 decline.

Methods

A detailed description of methods is provided in the online supplement.

Study population

The AREST CF program includes a comprehensive assessment of infants born with CF starting at 3 months and then annually until 6 years of age. Children are assessed at 2 pediatric CF centers: Perth Children's Hospital (PCH) formerly Princess Margaret Hospital for Children in Perth and the Royal Children's Hospital (RCH) in Melbourne. The study was approved by the ethics committee of each institution and written consent from parents was obtained at enrolment and at each follow-up.

Computed tomography and spirometry

A volume controlled, volumetric (since 2007 in Perth and 2010 in Melbourne) or limited slice (prior to 2007 and 2010) chest CT scan was obtained at end inspiration (Prs = 25cm H20) and end expiration (Prs = 0cm H2O) as described previously [11]. CT images were scored for the presence of structural lung disease using a simplified Brody CF-CT scoring method [10, 11].

Spirometry measurements performed during admissions or outpatient visits for the AREST CF cohort were obtained retrospectively, from PCH and RCH patient records, from 5 to 15 years of age. Spirometry was performed according to current ATS/ERS guidelines [17, 18]. For the years where more than one measurement was available per child, the annual best was selected for use in the analysis.

Statistical analyses

Approximately 10% of potential follow-up spirometry measurements between ages 5 to 15 years were not included in the analysis. Measurements were missing either because children were too young to provide technically acceptable results or for other technical reasons the attempts to provide a measurement were unacceptable. (see Figure 1 for detailed missing data information). In this study we report spirometric variables (FEV_1, FVC, FEV_1/FVC and FEF_{25-75}) as Z scores as recommended by the Global Lung Initiative [19].

The first step was to determine the optimal age at which the chest CT scan was the most clinically informative and most predictive of future lung function. Children were divided into 3 categories: 1-2 years old, 3-4 years old and 5-6 years old. Total CF-CT score in each age category was calculated as a sum of 4 sub-scores (trapped air, mucus plugging, bronchiectasis and bronchial wall thickening) and was divided into medians. While there were children that had a CT scan available in each age group, there was only 1 CT scan per child per age group. Observation time was defined as a 10-year period (5-15 years of age) and was of equal length for each age category. Lung function over time was assumed to follow a model of accelerated decline (i.e. with increasing age, the probability of children's lung function falling below defined Z

score threshold increases), therefore Weibull regression was used to calculate hazard ratios (HR). For the ease of clinical interpretation, HRs compared the time until FEV_1 Z scores fell below the lower limit of normal (that is -1.64 Z scores) [20] for above versus below the median of total CF-CT score during the observation period (see Figure 2). Sensitivity analysis was also performed by including total CF-CT score as a continuous variable (instead of a binary variable) (see eTable 8).

For the most predictive CF-CT score age, linear mixed effects models with random intercepts and slope subject effects and auto-regressive (lag 1) residual structure were fitted for spirometry Z scores as continuous outcomes and CF-CT scores as exposures of interest (see Tables 2, eTables 3, 4 and 5). Sensitivity analysis was also performed to asses if removal of participants that only had 1 or 2 follow-up spirometry measurements has an effect on the results (see eTable 2 a) and b)). BMI for age Z score was modelled similarly as additional clinical outcome of interest (see eTable 6). We performed additional sensitivity analyses by dividing participants in 2 groups by presence/absence of different sub-components and calculating the rate of decline in each group (see eTable 7).

The percentage of variation in future FEV_1 that was additionally explained by each structural sub-score was also assessed by fitting a series of multivariate cross-sectional regression models over a 5-year period. The results were compared with percentage of variation that was explained by earlier FEV_1 measurement (i.e. percentage of variation explained by FEV_1 at age 5-6 years in FEV_1 outcomes at ages 6-11 years) (see Figure 3).

All model coefficients are presented unadjusted and adjusted for previously published confounding variables: homozygous Phe508del mutation, pancreatic insufficiency, gender, time elapsed between CT scan and spirometry and test centre.

BMI for age Z scores were calculated according to WHO reference equations [21]. All analyses were performed using Stata v14 [22].

Results

Study population

In the period that chest CT scans have been included in the follow-up a total of 325 children were included in the AREST CF cohort, with 196 children having at least 1 annual spirometry measurement between the ages of 5 and 15 years. Of those 196 children, 48.47% were male with mean age of 3.67 (0.21) years during AREST CF CT accrual period and 52.14% were homozygous for the Phe508Del mutation. There was a total of 697 annual spirometry measurements available for the AREST CF cohort beyond the CT acquisition period from the combination of 2 sources (PCH and RCH), with a mean annual number of measurements per child being 4.79 (3.36). Of those 697 measurements, the mean age of acquisition was 9.30 (2.11) years. Mean FEV_1 and BMI for age Z scores at age of 5 years were -0.07 (1.23), 0.44 (0.90) and -1.11 (1.57), -0.85 (0.75) respectively at age 15 years.

There was an increasing prevalence of structural lung disease over the first 6 years of life (eFigure 1a), most notably bronchiectasis (prevalence increased from 33.1% individuals at ages 1-2 years to 73.7% at ages 5-6 years respectively) and mucus plugging (from 7.91% at ages 1-2 years to 37.13% at ages 5-6 years). Mean FEV_1 at

5-6 years was within normal range with approximate start of decline at the ages of 10-12 years (see Table 1 and eFigure 1b), while BMI for age Z score showed slow but nearly linear decline over the 10-year period (see eFigure 1c).

Determining the optimal age to perform a CT scan in early childhood

During the 10-year observation period 10.04% (70/697) of annual spirometry measurements of FEV_1 fell below the lower limit of normal threshold. Unadjusted and adjusted HRs comparing the time until FEV_1 fell below the threshold in children that had total CF-CT scores above versus below the median at different ages increased as children got older. At ages 1-2 years, adjusted hazard ratios (aHR) of time before FEV_1 Z score fell below -1.64 Z scores was 1.09 (0.43, 2.76) p=0.863, at 3-4 years aHR was 1.55 (0.63, 3.78) p=0.338 and at ages 5-6 years, children were nearly 3 times more likely to have their FEV_1 Z score fall below -1.64 (aHR 2.67 (1.06, 6.72) p=0.037) if their total CF-CT score was above the median (see Figure 2).

Sensitivity analysis including a total CF-CT score as a continuous variable reaches the same conclusion and shows that for every 1 point increase in CF-CT score, the aHR increased by (1.06 (1.02, 1.11) p=0.007) (see eTable 8).

Prediction of lung function trajectory based on different structural abnormalities detected at 5 to 6 years

Total CF-CT score at 5-6 years was predictive of FEV_1 (adjusted -0.02 (-0.04, -0.01) p=0.006), FVC (adjusted -0.02 (-0.03, -0.00), p=0.044) and BMI for age Z score decline (adjusted -0.02 (-0.03, -0.00) p=0.017) for each 1 point increase in CF-CT score (see Table 2, eTables 2, 3, 4, 5 and 6).

Of all structural abnormalities, the extents of mucus plugging and trapped air were most strongly associated with FEV_1 decline during the observation period. In adjusted analysis mucus plugging and trapped air were also significantly associated with FVC and FEF_{25-75} Z scores (see eTables 1, 2 and 3).

The extent of mucus plugging and bronchiectasis were the only chest CT abnormalities (apart from total CF-CT score) that were significantly predictive of BMI for age Z score decline (-0.10 (-0.18, -0.02) p=0.017 and -0.04 (-0.08, 0.01) p=0.022 respectively) in adjusted analysis (see eTable 4). Additionally, in a sensitivity analysis, out of all the sub-scores, presence or absence of any mucus plugging on a CT scan at ages 5-6 years best discriminated the difference in FEV_1 rate of decline in the next 10 years of life, with the rate of the decline in the presence and absence groups (-0.08 (-0.14, -0.01) p=0.017 and -0.00 (-0.07, 0.06) p=0.903) p=0.903) respectively is (see Figure 3 and eTable 5).

Percentage of future FEV_1 explained by different structural abnormalities detected at 5 to 6 years

The predictive power of CT scores in young children is consistently stronger the more time elapses between initial CT scan and spirometry measurement in multivariate models (mucus plugging score at 5-6 explains only 3% of additional variation in FEV_1 Z score at the same age but over 40% of additional variation 5 years later) while the opposite is true for FEV_1 Z score (at age 5 it explains nearly 38% of additional variation in FEV_1 a year later but under 20% of additional variation 5 years later) (see Figure 4). A similar pattern is seen in other structural

abnormalities. These results suggest that while FEV_1 is a better predictor of future FEV_1 in the short term, CT abnormalities such as mucus plugging and trapped air are better predictors of longer term FEV_1. Spirometry measured FEV1 remains a better predictor of future FEV1 than bronchiactesis and bronchial wall thickening through the entire observation period.

Discussion

In this retrospective analysis of prospectively collected standardised data from the AREST CF cohort, we observed a strong relationship between structural lung disease in children under 6 years of age and longer term clinical outcomes. We found that extent of mucus plugging and trapped air at ages 5-6 years were strongly predictive of mean FEV_1 decrease over the next 10 years. A unique and important observation was that CT scan evidence of mucus plugging at ages 5-6 years was the only structural abnormality that showed a significant difference in rate of FEV_1 Z score decline between presence and absence groups.

AREST CF is a large pediatric CF cohort that is characterized by comprehensive prospective follow-up that includes annual or biennial CT scans from two Australian CF centres with comparable clinical management practices. We utilized data collected as a part of routine outpatient clinic visits after the end of the formal AREST CF early surveillance period (age of 6 years), that enabled us to examine in an unbiased manner, retrospective data collected prospectively that we hypothesized would predict long term clinical outcomes. Results and conclusions in this study are robust and consistent across many different modelling approaches and when using different outcome and predictor thresholds as was shown in our sensitivity analyses.

Other studies have been published that investigated relationships between CT and spirometry outcomes but assessed disease tracking comparison in a cross-sectional manner rather than longitudinal prediction of the future disease trajectory. The largest study published in 2006 [14], with 119 participants compared the rate of progression of lung disease on serial CT scans and spirometry measurements in groups of children and adults and found them to be discordant with bronchiectasis being the most reliable marker of disease progression. A study in 2004 [7] by the same group investigated paired high resolution CT scans and spirometry tests in children of mean age of 11 years at the first test and aimed to asses tracking of disease progression over a 2-year period. Their results are consistent with AREST CF data and demonstrated that mucus plugging and bronchiectasis are two components that progressed most while additionally highlighting that spirometry remained stable during the same period.

One of the interesting and perhaps counter-intuitive findings in our study was that the predictive ability of mucus plugging and to the lesser extent trapped air was stronger than that of bronchiectasis which is considered a feature of irreversible lung damage. A possible explanation is that both trapped air and mucus plugging reflect an active disease process, with mucus plugging being an independent and persistent driver of inflammation and future airway damage, whereas bronchiectasis is an endpoint reflecting prior pathological processes. Recent publications [23-25] support the hypothesis that airway surface dehydration due to cystic fibrosis transmembrane conductance regulator (CFTR) gene dysfunction leads to excessive mucus production which triggers chronic neutrophilic inflammation and structural lung

damage (Esther et al. Science Trans Med 2019. In Press). Our data suggest that interventions that minimise mucus plugging are likely to have a significant effect on future lung disease trajectories.

Another important finding is the additional evidence for revising current guidelines for data collection in CF registries worldwide. Most registries currently only report respiratory data from age 6 onwards, focusing on the age when spirometry starts to be routinely performed in CF centres. Even though many imaging studies [7, 26-30] have presented compelling evidence of early onset and progression of lung disease, CT scan data are not routinely collected nor included in registries. We have identified a time period, in children aged 6 or under, during which a CT scan gives important clinical information and that shows a clear relationship with later functional outcomes. Additionally, we found that structural sub-components are more predictive of functional trajectories 5 years later than lung function itself when measured at the same age. This suggests that besides CT providing additional important information regarding an individual's current clinical status, it can be used to identify children that are most at risk of worse clinical outcomes later in life. Therefore, a goal for CF centres could be the standardised acquisition of a single chest CT at 5 years of age.

Due to limited CF populations available for traditional randomized controlled trials there is a need for new approaches to determine effectiveness of interventions as they become available. Our results provide a strong rationale for including CT outcomes at age 5-6 years in CF registries. Including childhood CT outcomes in CF registries would allow evaluations of the impact of new interventions in early life at an

age before extensive lung damage has occurred and the likely impact on adult lung function which is associated with long term morbidity and mortality [31].

Low dose radiation scans are considered safe and at 5-6yrs of age, satisfactory images can be obtained without a general anaesthetic [32]. Further analysis of the AREST CF longitudinal data and outcomes from current intervention studies (COMBATCF NCT01270074 and SHIP-CT NCT02950883) that use CT as primary endpoints will provide additional information regarding the CT outcomes of most value.

Two approaches have been published recently that might be more sensitive for detecting mild changes in lung structure than the CF-CT approach used in this study: PRAGMA-CF [33] and airway:artery ratio [6]. However, since these techniques involve new methods to image capture and analysis, there were insufficient CT images acquired that could be linked with long term FEV_1 follow-up measurements. A limitation of PRAGMA-CF is that because it is a hierarchical scoring system the independent effects on FEV_1 of structural changes such as mucous plugging cannot be assessed. To increase the duration of follow-up, maximize the overall sample size, and investigate the individual role of mucus plugging, we therefore used the CF-CT score in our analyses. Going forward, PRAGMA CF is a more discriminative marker of overall structural lung damage and a fully automated tool is in development and should be available in the near future . The PRAGMA CF score will provide clinicians with a validated outcome that assesses progression of mild disease that is not possible using spirometry. Therefore, clinicians should be able to better stratify high risk patients for more intensive therapy.

We acknowledge that validation of our results in an independent cohort should be undertaken. In the meantime, we believe that our data are likely to be representative [34] and difficult to replicate in the near future due to sample size requirements and the unique nature of the AREST CF program. We also acknowledge that while this data is based on a group of children and is useful for stratification of groups at risk, use of absolute Brody CF-CT scores as a clinical tool for an individual screening should not be over-interpreted.

In conclusion, both bronchiectasis and non-bronchiectatic lung abnormalities in young children with CF are important markers of disease severity and predictors of future lung disease progression. The extent of mucus plugging at ages 5 to 6 years provides a simple stratification tool that can identify children at increased risk of poor outcomes in later life and is an early indicator of the effectiveness of interventions in very young children that have disease modifying potential.

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Table 1. Clinical characteristics of children enrolled in AREST CF for which CT scans were available.

	1-2 years	3-4 years	5-6 years
Age	1.66 (0.20)	3.68 (0.21)	5.66 (0.21)
Gender (Male)	70/139 (50.36%)	81/162 (50.00%)	82/167 (49.10%)
Test centre (Perth: Melbourne)	72/139 (51.80%)	79/162 (48.77%)	67/167 (40.12%)
Genotype			
Homozygous Phe508del/Phe508del	71/139 (51.08%)	85/158 (53.80%)	83/161 (51.55%)
Heterozygous Phe508del/other	64/139 (46.04%)	68/158 (43.04%)	71/161 (44.10%)
Meconium ileus	27/134 (20.15%)	30/156 (19.23%)	31/158 (19.62%)
Pancreatic sufficient	20/139 (14.39%)	25/162 (15.43%)	25/164 (15.24%)
PSA culture positive	14/139 (10.07%)	20/162 (12.35%)	22/167 (13.17%)
Structural lung disease			
Bronchiectasis presence	46/139 (33.09%)	98/162 (60.49%)	123/167 (73.65%)
Trapped air presence	106/139 (76.26%)	99/162 (61.11%)	127/167 (76.05%)
Mucus plugging presence	11/139 (7.91%)	44/162 (27.16%)	62/167 (37.13%)
Bronchial wall thickening presence	106/139 (76.26%)	142/162 (87.65%)	154/167 (92.22%)
Spirometry measured lung function at 5 to 6 years			
FEV_1 Z score	-0.06 (1.19)	-0.08 (1.24)	-0.10 (1.24)
FVC Z score	0.57 (1.18)	0.57 (1.22)	0.65 (1.19)
FEV_1/FVC Z score	-0.70 (0.98)	-0.70 (1.01)	-0.75 (0.99)
FEF_{2575} Z score	-0.35 (1.17)	-0.33 (1.18)	-0.34 (1.18)

Scans were divided into age groups, with only a single scan per child in each age group. There are multiple scans of the same child in different age groups. Data are presented as p/n (%) or mean (standard deviation).

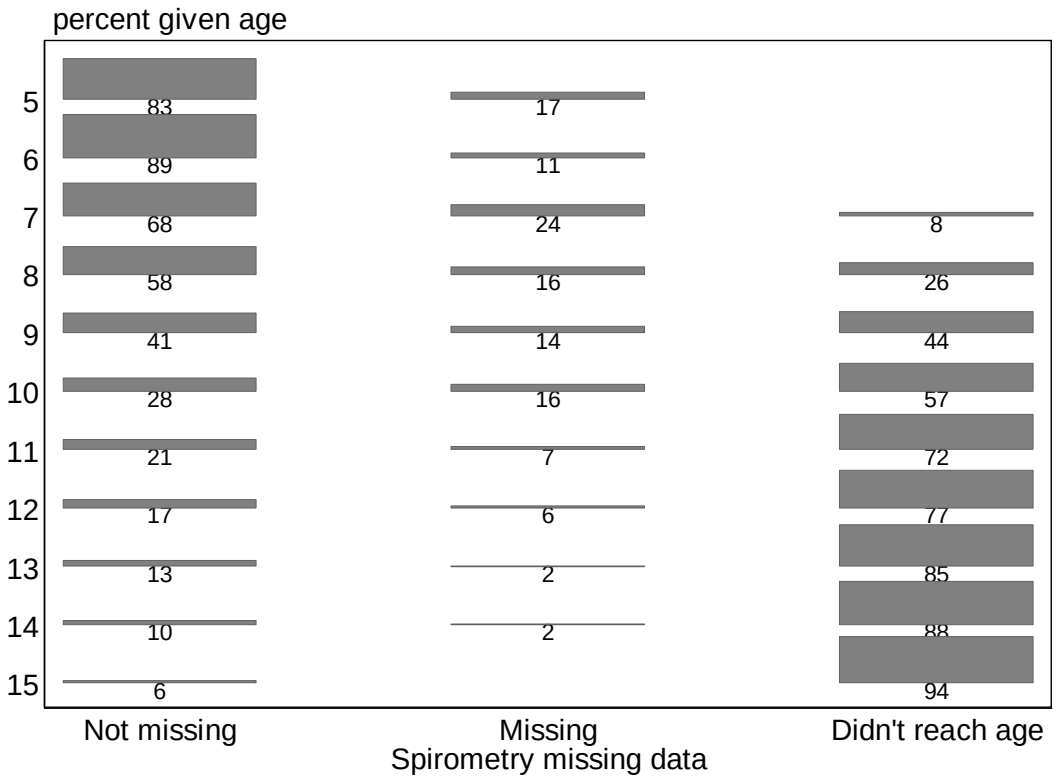
Table 2. Structural predictors of FEV_1 Z score decline

CF-CT extent score at age 5-6 years	Mean change (95% CI) p-value (unadjusted) n=697	Mean change (95% CI) p-value (adjusted*) n=663
Mucus plugging	**-0.19 (-0.29, -0.09) p<0.001**	**-0.17 (-0.26, -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=0.021**	-0.04 (-0.08, 0.00) p=0.051
Bronchial wall thickening	-0.02 (-0.07, 0.03) p=0.450	-0.01 (-0.05, 0.04) p=0.734
Total score	**-0.03 (-0.05, -0.01) p=0.001**	**-0.02 (-0.04, -0.01) p=0.006**

Data was presented for 167 children that had a CT scan available at ages 5-6 years and a total of 697 annual spirometry measurements in the following 10 years.

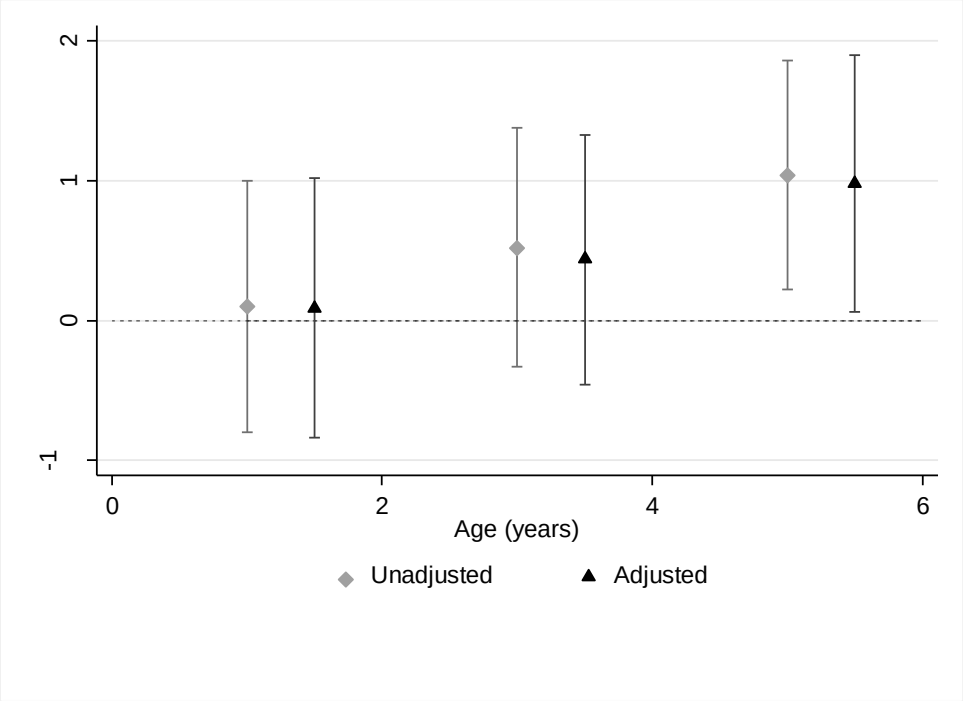
* Models were adjusted for: intrinsic disease severity (Homozygous D508 mutation, pancreatic sufficiency and gender), test centre and age at spirometry.

Figure 1. Percentage of missing spirometry data at each age group



In 2016, 94% of AREST CF cohort that had CT scan available at ages 5-6 years were younger than 15 years.

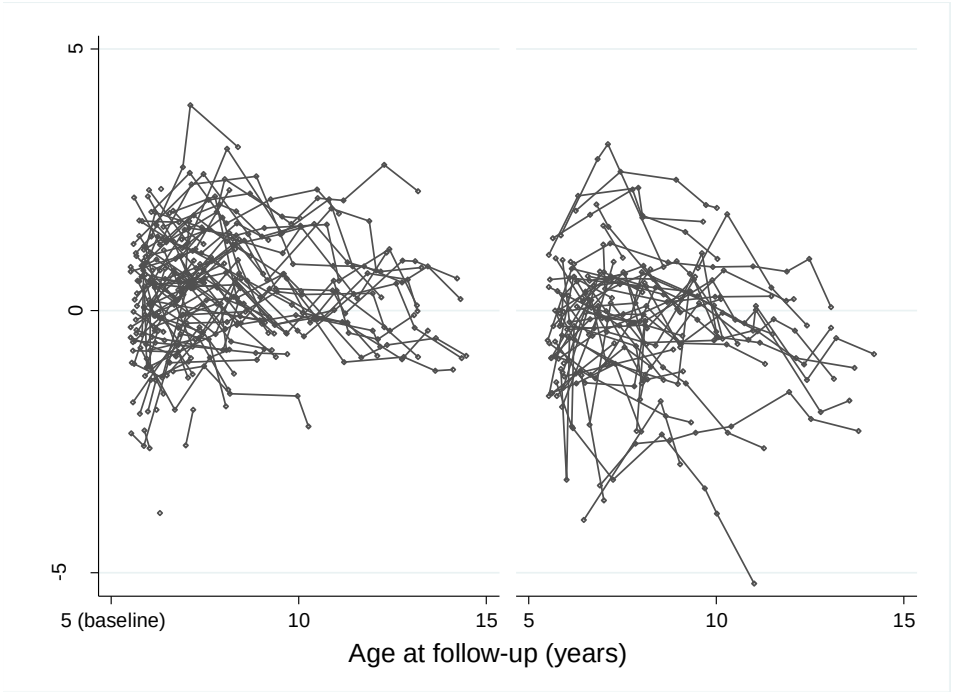
Figure 2. Adjusted hazard ratios of FEV_1 falling below 1.64 Z scores during the 10 years of observation time with total CF-CT score being above vs below the median at different ages.



Hazard ratios were presented on the log scale. Cox regression was adjusted for intrinsic disease severity (Homozygous D508 mutation, pancreatic sufficiency, meconium ileus and gender), test centre and time between CT scan and spirometry.

Figure 3. FEV_1 trajectories based on presence of mucus plugging on a CT scan at ages 5 to 6 years.

a)



b)

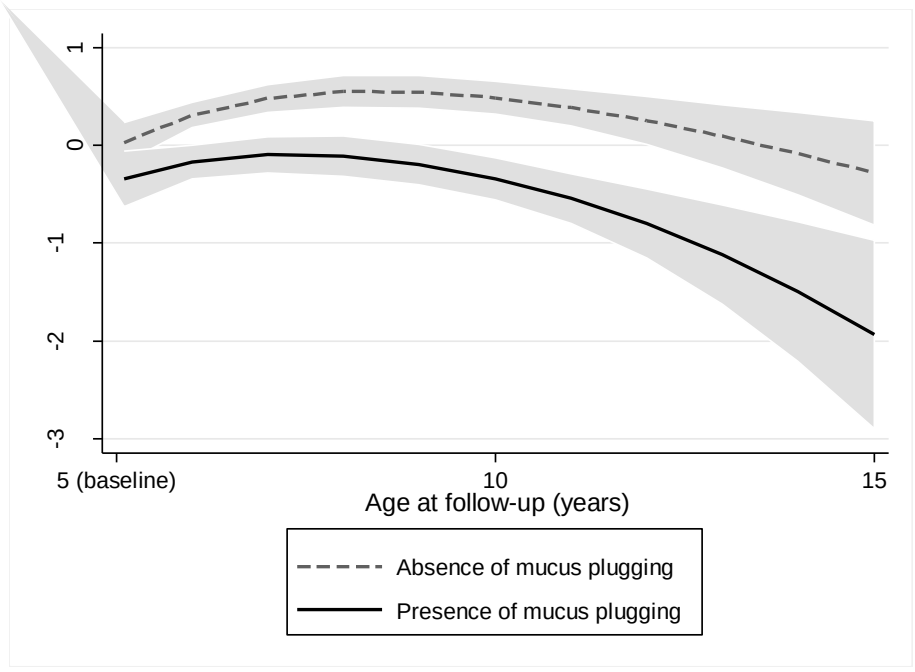


Figure 3 a) represents individual FEV_1 trajectories of children that had no mucus plugging detected on a CT scan on the left and those that did on the right at ages 5-6 years. Figure 3 b) represents best fit fractional polynomial curves for both scenarios with corresponding 95% confidence intervals.

Figure 4. Percentage of FEV_1 variation explained by different predictors at 5-6 years in the next 5 years of life.

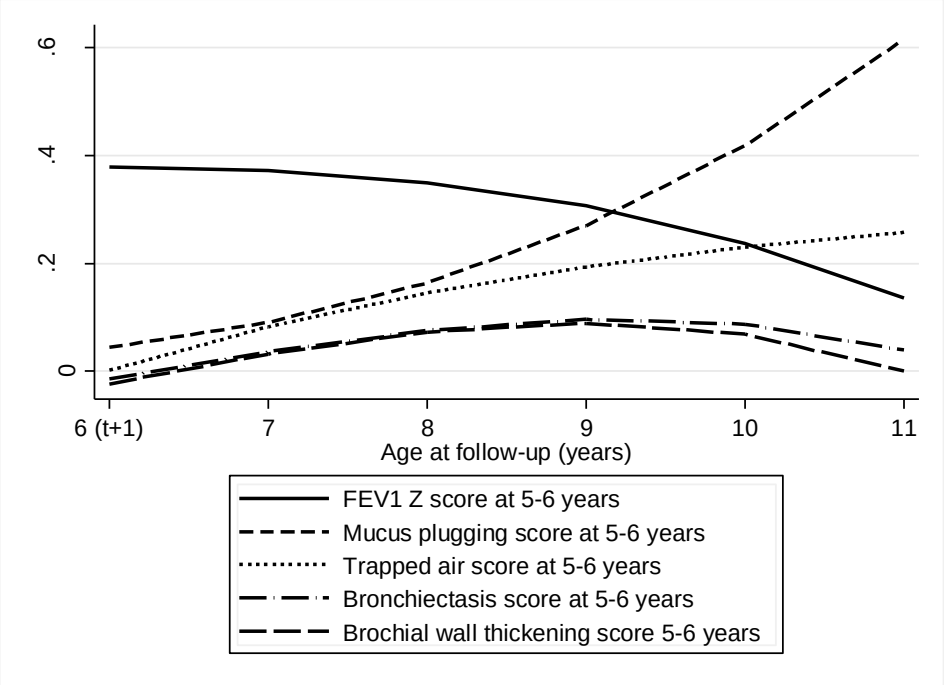


Figure 3 represents adjusted R^2 in a series of multivariate cross-sectional regression models fitted to FEV_1 at ages 6-11 as outcomes (one at the time). Base model R^2 was first calculated for previously defined confounding variables. Additional R^2 was then determined by adding the main exposure of interest to the base model and calculating the difference. Ages where models had data from less than 30 individuals were excluded from analysis due to instability of model estimates.

Online Data Supplement

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

Authors: Lidija Turkovic, Daan Caudri, Tim Rosenow, Oded Breuer, Conor Murray, Harm AWM Tiddens, Fiona Ramanauskas, Sarath C Ranganathan, Graham L Hall, Stephen M Stick

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 H20) 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.

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9. StataCorp, *Stata Statistical Software: Release 14. .* College Station, TX: StataCorp LP, 2015.

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

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

eTable 2. Sensitivity analysis for structural predictors of FEV_1 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 FEVFVC Z score decline based on a CT scan available at ages 5-6 years and annual spirometry measurements in the following 10 years.

ZFEVFVC	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 $ZFEF_{2575}$ 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 FEV_1 Z score decline per year in presence/absence of different structural abnormality groups.

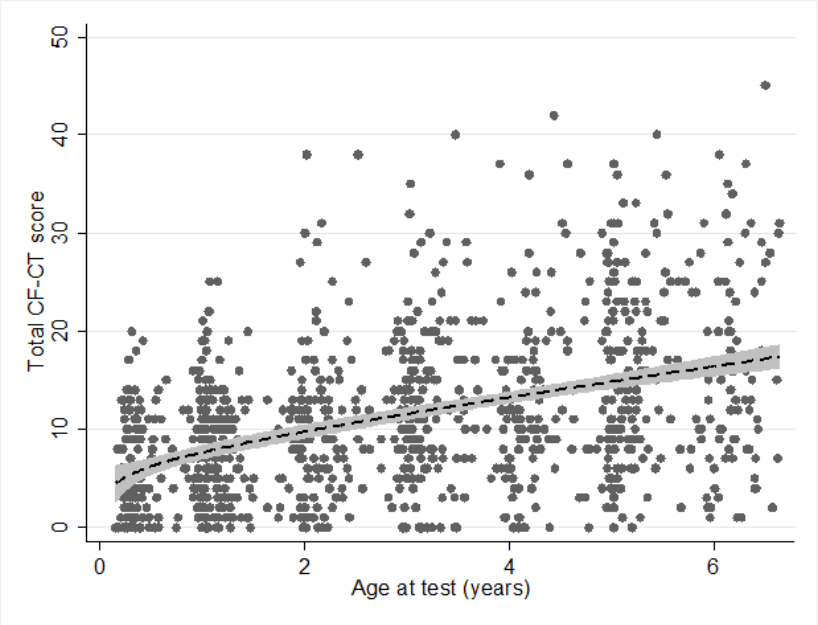
CF-CT presence at age 5-6 years	Abnormality absent Rate of decline per year (95% CI) p-value	Abnormality present Rate of decline per year (95% CI) p-value
Mucus plugging	-0.00 (-0.07, 0.06) p=0.903	**-0.08 (-0.14, -0.01) p=0.017**
Trapped air	-0.03 (-0.11, 0.05) p=0.486	**-0.07 (-0.11, -0.02) p=0.004**
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 FEV_1 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 FEV_1 through adolescence using linked data (c) Decline of WHO BMI for age Z score through adolescence using linked data.

a)



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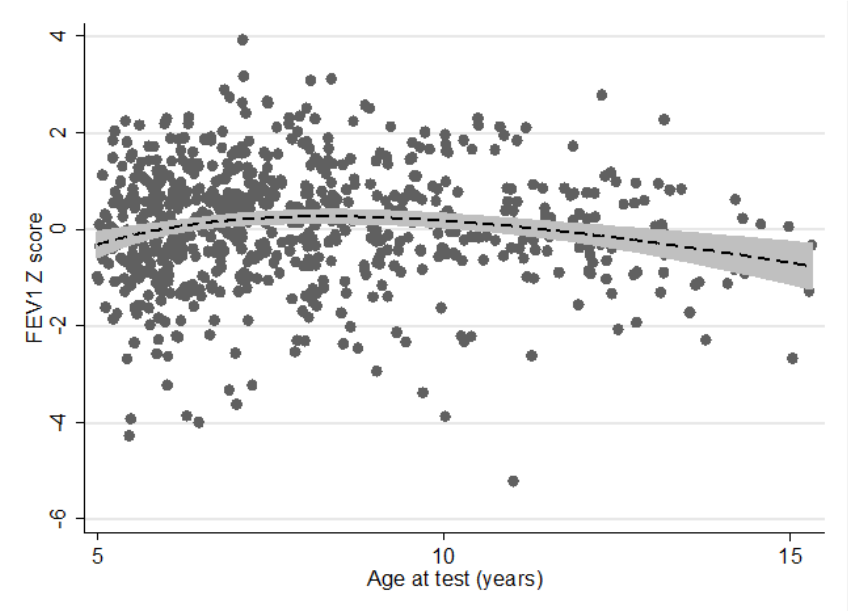
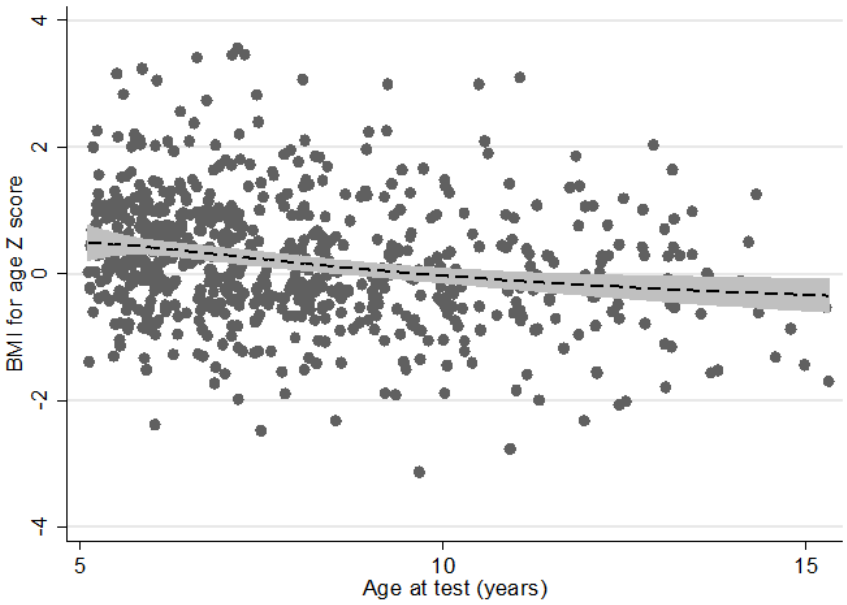


c)


BMI for age Z score
4
2
0
-2
-4
5
10
15
Age at test (years)