Association of lung clearance index with survival in individuals with cystic fibrosis

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Tables

Table S1: Definitions of variables in baseline and sensitivity analyses.

Sex	Gender, binary (0: female, 1: male)
Age at CF diagnosis	Individuals age at CF diagnosis in years
Mutation	Individuals homozygote for F508del (0), *individuals heterozygote for F508del (1),* individuals with any other mutation (2)
Test date	Date (yyyy/mm/dd) of the third MBW measurement out of the three MBW measurements within the first three years after study entry; begin of crude mortality time
Age, height, weight, BMI	Values from test date (age: years, height: meters, weight: kg, BMI: z-score)
Person-years	Person-years takes the number of individuals and the amount of time each single individual spent under risk of experiencing the outcome, death or LTX, into account. As CF is a genetic disorder, the origin of "time under risk" started at birth (zero years of age) in this study
LCI	*Baseline*: First available MBW measurement as baseline value *Sensitivity analysis:* Mean of the first three LCI values within the first three years after study entry (= first available MBW measurement) as baseline value and exclusion of individuals with less than three measurements within the first three years after study entry
FEV$_1$	*Baseline*: FEV$_1$ value that was reported corresponding to the first available LCI value (FEV$_1$ and LCI were measured at the same day)

	Sensitivity analysis: Mean of the three FEV_1 values that were reported corresponding to the first three available LCI values within the first three years after study entry
Hospitalisations	Count of all hospitalisations reported in the electronic patient charts within the first three years after study entry
Exacerbations	Count of all exacerbations reported in the electronic patient charts within the first three years after study entry
Pancreatic insufficiency	Pancreatic insufficiency at least once reported/ diagnosed within the frist three years after study entry "yes – 1", otherwise "no - 0"
CFRD	CFRD at least once reported/ diagnosed within the first three years after study entry "yes – 1", otherwise "no - 0"
ABPA	ABPA at least once reported/ diagnosed within the first three years after study entry "yes – 1", otherwise "no - 0"
Microbiology	Pseudomonas aeruginosa at least once reported/ diagnosed within the first three years after study entry "yes – 1", otherwise "no – 0"
	Staphylococcus aureus at least once reported/ diagnosed within the first three years afters study entry "yes – 1", otherwise "no – 0"
Medication	At least once treated with any antibiotics (oral, iv, inhaled) within the first three years after study entry "yes – 1", otherwise "no – 0"
	At least once treated with any inhaled medication (mucolytics, bronchodilators, steroids) within the first three years after study entry "yes – 1", otherwise "no – 0"
Outcome (death or LTX)	Date (yyyy/mm/dd) of death or of lung transplantation as reported in the electronic patient charts (1) versus survival (0). Survival means the patient was alive until the end of the study in 2018/12/31, e.g. when the patient had at least one follow-up visit after 2018/12/31

Legend Table S1: *Abbreviations***:** ABPA = Allergic bronchopulmonary aspergillosis, BMI =

Body mass index, CF = Cystic fibrosis, CFRD = Cystic fibrosis-related diabetes, FEV_1 = Forced

expired volume in the first second, LCI = Lung clearance index, LTX = Lung transplantation

Table S2: Population characteristics of individuals stratified by endpoint.

	Death	LTX	Alive	Lost to follow-up
n [females, %]	41 [22, 53.7]	53 [27, 50.9]	128 [54, 42.2]	15 [10, 66.7]
LCI (units)	17.2 [7.3; 3.9 – 46.6]	18.9 [8.4; 5.6 – 59.8]	16.9 [6.6; 3.5 – 47.2]	19.0 [9.2; 9.3 – 41.2]
LCI (z-score)	8.3 [7.3; - 5.0 – 37.7]	10.0 [8.4; -3.3 – 50.9]	8.0 [6.6; -5.4 – 38.3]	10.1 [9.2; 0.4 – 32.3]
FEV$_1$ (z-score)	-3.7 [1.9; -6.3 – 0.8]	-3.1 [1.8; -6.1 – 0.4]	-1.6 [1.6; -5.6 – 1.7]	-3.5 [1.9; -6.4 – -0.5]
Year of birth	1974 [9.4; 1952 – 1991]	1980 [8.7; 1960 – 1997]	1988 [9.8; 1955 – 2000]	1980 [7.7; 1963 – 1990]
Age at baseline (years)	19.7 [9.7; 6.0 – 41.0]	15.0 [7.4; 5.9 – 34.2]	11.4 [7.1; 5.6 – 40.2]	15.8 [6.4; 6.9 – 26.1]
BMI (z-score)	-1.3 [1.2; -4.0 – 0.3]	-1.2 [1.0; -4.0 – 1.4]	-0.5 [1.0; -3.4 – 2.4]	-1.4 [1.1; -4.0 – 0.0]
Age at outcome (years)	32.0 [10.8; 9.0 – 50.0]	28.8 [9.0; 15.0 – 47.0]	30.4 [9.8; 18.0 – 63.0]	25.3 [11.4; 8.0 – 44.0]

Legend Table S2: Data presented as mean [SD; range], unless indicated otherwise.

Abbreviations: BMI = Body mass index, FEV$_1$ = Forced expired volume in the first second,

LCI = Lung clearance index.

Table S3. Risk of death or lung transplantation according to baseline lung function.

	LCI	FEV$_1$
Crude model	1.04 [1.01 – 1.06]	1.25 [1.11 – 1.41],
Mutual model	1.03 [1.00 – 1.06]	1.22 [1.08 – 1.38]
Complete model	1.03 [1.00 – 1.06]	1.15 [0.97 – 1.36]
Reduced model	1.04 [1.01 – 1.07]	1.18 [1.01 – 1.38]
Final model	1.04 [1.01 – 1.07]	1.12 [0.95 – 1.33],

Legend Table S3: Crude and adjusted Hazard Ratios [95% CI] for the risk of death or lung transplantation using the first available LCI and corresponding FEV$_1$ value as baseline. *Definitions:* Crude model: unadjusted HR per one z-score increase in LCI and one z-score decrease in FEV$_1$; Mutual model: HR per one z-score increase in LCI and one z-score decrease in FEV$_1$, adjusted mutually; Complete model: HR per one z-score increase in LCI and per one z-score decrease in FEV$_1$ adjusted separately for all demographic and clinical variables (sex, age, BMI, year of birth, number of hospitalisations, number of exacerbations, mutation, pancreatic insufficiency, CFRD, ABPA, microbiology, medication), Reduced model: Adjusted HR per one z-score increase in LCI and one z-score decrease in FEV$_1$, adjusted for the selected variables sex, age, BMI, year of birth, number of hospitalisations; Final model: HR per one z-score increase in LCI and per one z-score decrease in FEV$_1$, adjusted mutually in addition to the aforementioned variables. *Abbreviations*: ABPA = Allergic bronchopulmonary aspergillosis, BMI = Body mass index, CF = Cystic fibrosis, CFRD = Cystic fibrosis-related diabetes, CI = Confidence interval, FEV$_1$ = Forced expired volume in the first second, HR = Hazard ratio, LCI = Lung clearance index, LTX = Lung transplantation.

Table S4: Population characteristics in individuals with normal FEV$_1$ and in adults.

	Individuals with normal FEV$_1$ ($\geq$ - 1.96 z-score)	**Adults > 16.0 years of age)**
n [females, %]	108 [55, 50.9]	69 [35, 50.7]
Year of birth	1988 [9.2; 1955 – 2000]	1970 [6.8; 1952–1988]
Median age at CF diagnosis [IQR, range]	1.0 [0.0 – 2.0; 0.0 – 14.0]	1.0 [0.0–3.0; 0.0–28.0]
Age (years)	10.4 [6.2; 5.6 – 40.2]	24.8 [6.5; 16.1–41.0]
BMI at study entry (z-score)	-0.4 [1.0; -4.2 – 2.4]	-1.1 [1.2; -4.2–0.4]
LCI (z-score)	7.3 [7.5; -5.4 – 50.9]	8.3 [6.8; -5.0 – 32.3]
FEV$_1$ (z-score)	-0.56 [0.9; -1.9 – 1.7]	-3.8 [1.8; -6.4–0.4]
Outcome (Death or LTX), n [%]	24 [22.2]	40 [58.0]
Loss to follow-up, n [%]	4 [3.7]	7 [10.1]

Legend Table S4: Data presented as mean [SD, range], unless indicated otherwise. *Definitions:* Baseline = First available LCI and corresponding FEV$_1$ value demographic and clinical data derived within the first three years after study entry; *Abbreviations*: BMI = Body mass index, CF = Cystic fibrosis, FEV$_1$ = Forced expired volume in the first second, LCI = Lung clearance index, LTX = Lung transplantation.

Table S5: Risk of death or lung transplantation individuals with normal FEV$_1$ and in adults.

	Individuals with normal FEV$_1$ ($\geq$ - 1.96 z-score)	Adults (> 16.0 years of age)
n	108	69
LCI		
Crude model	1.02 [0.97 – 1.08]	1.01 [0.96 – 1.06]
Mutual model	1.03 [0.98 – 1.08]	0.98 [0.92 – 1.03]
Complete model	1.01 [0.96 – 1.07]	1.01 [0.94 – 1.09]
Reduced model	1.02 [0.97 – 1.07]	1.00 [0.95 – 1.06]
Final model	1.03 [0.98 – 1.09]	0.97 [0.91 – 1.04]
FEV$_1$		
Crude model	0.99 [0.61 – 1.61]	1.33 [1.07 – 1.65]
Mutual model	0.96 [0.58 – 1.57]	1.37 [1.09 – 1.72]
Complete model	0.68 [0.35 – 1.31]	1.22 [0.92 – 1.62]
Reduced model	0.76 [0.43 – 1.36]	1.26 [0.96 – 1.64]
Final model	0.71 [0.40 – 1.29]	1.33 [0.99 – 1.79]

Legend Table S5: Crude and adjusted Hazard Ratios [95% CI] for the risk of death or lung transplantation in individuals with normal FEV$_1$ ($\geq$ - 1.96 z-score) and adults ($\geq$ 16.0 years of age) using the first available LCI and corresponding FEV$_1$ value as baseline. *Definitions:* Crude model: unadjusted HR per one z-score increase in LCI and one z-score decrease in FEV$_1$; Mutual model: HR per one z-score increase in LCI and one z-score decrease in FEV$_1$, adjusted mutually; Complete model: HR per one z-score increase in LCI and per one z-score decrease in FEV$_1$ adjusted separately for all demographic and clinical variables (sex, age, BMI, year of birth, number of hospitalisations, number of exacerbations, mutation, pancreatic insufficiency,

CFRD, ABPA, microbiology, medication), Reduced model: Adjusted HR per one z-score increase in LCI and one z-score decrease in FEV_1, adjusted for the selected variables sex, age, BMI, year of birth, number of hospitalisations; Final model: HR per one z-score increase in LCI and per one z-score decrease in FEV_1, adjusted mutually in addition to the aforementioned variables. *Abbreviations*: ABPA = Allergic bronchopulmonary aspergillosis, BMI = Body mass index, CF = Cystic fibrosis, CFRD = Cystic fibrosis-related diabetes, CI = Confidence interval, FEV_1 = Forced expired volume in the first second, HR = Hazard ratio, LCI = Lung clearance index, LTX = Lung transplantation.

Table S6: Fully adjusted Cox proportional hazards regression model.

	HR	P	[95% CI]
LCI (z-score)	1.033	0.030	1.003 – 1.064
FEV_1 (z-score)	1.099	0.294	0.921 – 1.310
Sex (0 = female, 1 = male)	0.486	0.003	0.302 – 0.783
Age (years)	0.892	0.002	0.830 – 0.958
BMI (z-score)	0.771	0.034	0.606 – 0.980
Year of birth	0.947	0.104	0.886 – 1.011
Age at CF-diagnosis	0.998	0.952	0.936 – 1.064
Mutation (0 = F508del homozygous, 1 = F508del heterozygous, 2 = Other)	1.027	0.910	0.652 – 1.615
Number of exacerbations	1.075	0.277	0.944 – 1.224
Number of hospitalisations	1.129	0.196	0.939 – 1.357
ABPA (1= yes, 0 = no)	1.595	0.238	0.734 – 3.466
Pseudomonas aeruginosa (1= yes, 0 = no)	1.148	0.637	0.606 – 2.176
Staphylococcus aureus (1= yes, 0 = no)	0.679	0.122	0.415 – 1.109
CFRD (1= yes, 0 = no)	0.873	0.693	0.444 – 1.715
Pancreas insufficiency (1= yes, 0 = no)	0.895	0.866	0.245 – 3.272
Antibiotic medication (1 = yes, 0 = no)	1.079	0.911	0.287 – 4.058

Legend Table S6: Estimates for the fully adjusted Cox proportional hazard regression model using the first available LCI and corresponding FEV_1 value as baseline. *Abbreviations:* ABPA = Allergic bronchopulmonary aspergillosis, BMI = Body mass index, CF = Cystic fibrosis, CFRD = CF-related diabetes, CI = Confidence interval, FEV_1 = Forced expired volume in the first second, HR = Hazard ratio, LCI = Lung clearance index, P = P-value.
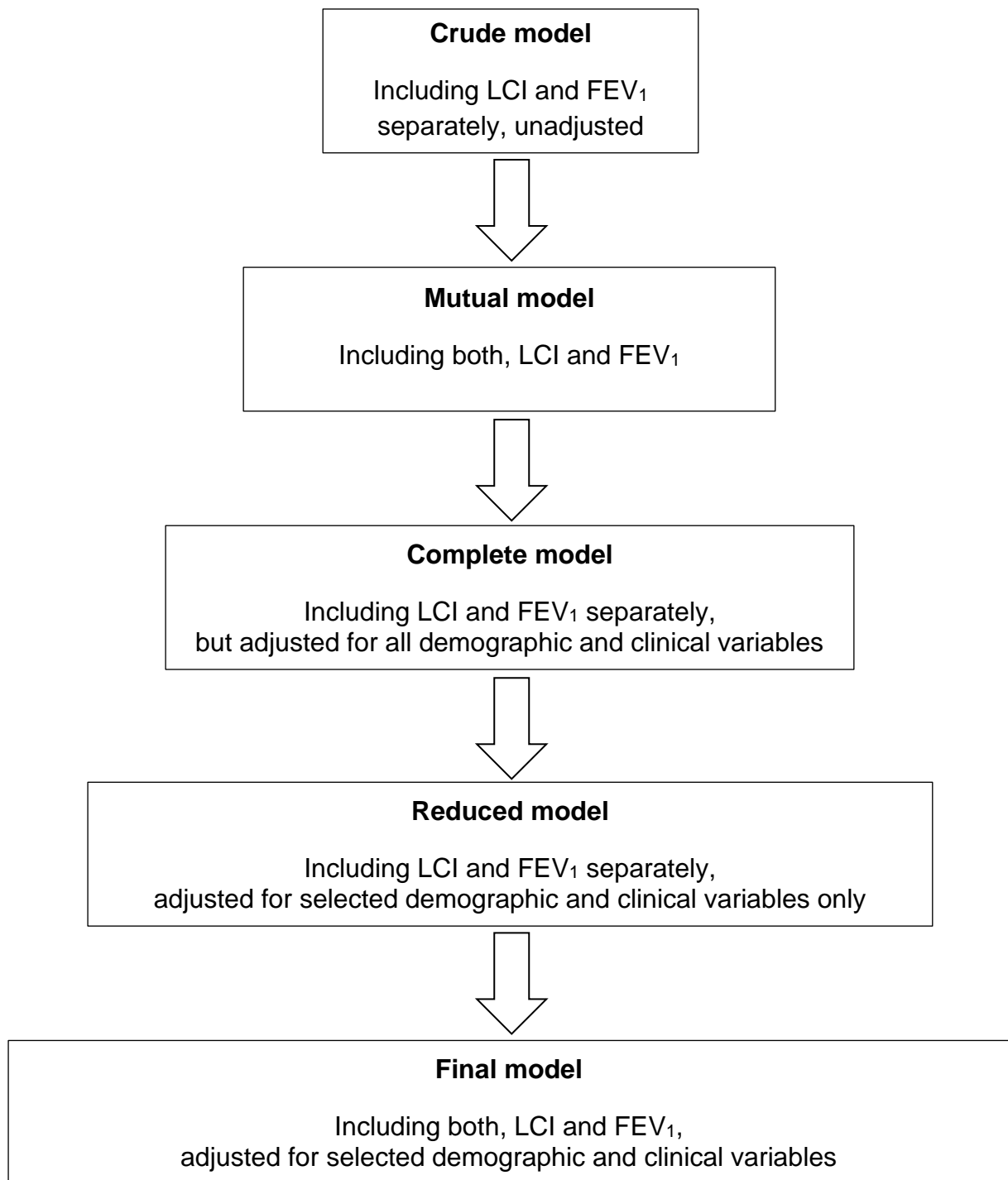
Table S7: Final Cox proportional hazards regression model.

	HR	P	[95% CI]
LCI (z-score)	1.037	0.011	1.008 – 1.066
FEV$_1$ (z-score)	1.124	0.164	0.953 – 1.327
Sex (0 = female, 1 = male)	0.570	0.011	0.370 – 0.878
Age (years)	0.907	0.005	0.847 – 0.971
BMI (z-score)	0.772	0.027	0.613 – 0.971
Year of birth	0.952	0.109	0.896 - 1.011
Number of hospitalisations	1.117	0.151	0.961 – 1.300

Legend Table S7: Estimates for the final Cox proportional hazards regression model using the first available LCI and corresponding FEV$_1$ value as baseline. Definition: Final model. HR per one z-score increase in LCI and one z-score decrease in FEV$_1$ adjusted mutually in addition to the selected variables (sex, age, BMI, birth year, number of hospitalisations). *Abbreviations:* BMI = Body mass index, CI = Confidence interval, FEV$_1$ = Forced expired volume in the first second, HR = Hazard ratio, LCI = Lung clearance index, P = P-Value

Figure legends

Figure S1. Analysis steps. *Crude model:* Unadjusted HRs per z-score increase in LCI and decrease in FEV$_1$. *Mutual model:* HR per z-score increase in LCI and decrease in FEV$_1$, adjusted mutually; *Complete model:* HR per z-score increase in LCI and decrease in FEV$_1$, adjusted separately for all demographic and clinical variables (sex, age, BMI, year of birth, mutation, age at CF diagnosis, infection burden, CFRD, ABPA, pancreas function, medication, number of exacerbations and hospitalisations); *Reduced model:* HR per z-score increase in LCI and decrease in FEV$_1$, adjusted separately for selected variables only (sex, age, BMI, year of birth, number of hospitalisations); *Final model:* HR per z-score increase in LCI and decrease in FEV$_1$, adjusted mutually in addition to selected variables (sex, age, BMI, year of birth, number of hospitalisations). ABPA = Allergic bronchopulmonary aspergillosis, BMI = Body mass index, CF = Cystic fibrosis, CFRD = Cystic fibrosis-related diabetes, FEV$_1$ = Forced expired volume in the first second, HR = Hazard ratio, LCI = Lung clearance index.

Crude model

Including LCI and FEV_1
separately, unadjusted

⬇

Mutual model

Including both, LCI and FEV_1

⬇

Complete model

Including LCI and FEV_1 separately,
but adjusted for all demographic and clinical variables

⬇

Reduced model

Including LCI and FEV_1 separately,
adjusted for selected demographic and clinical variables only

⬇

Final model

Including both, LCI and FEV_1,
adjusted for selected demographic and clinical variables

Figure S2. Respiratory survival in individuals with CF according to baseline FEV$_1$.
Individuals with baseline FEV$_1$ values $\geq$ study population median of -2.3 z-score, n = 119
(dashed line) vs. individuals with baseline FEV$_1$ values < study population median of -2.3 z-
score, n = 118 (solid line) using the first available FEV$_1$ value as baseline. CF = Cystic fibrosis,
FEV$_1$ = Forced expired volume in the first second, LTX = Lung transplantation, p = 0.50: 50%
of the individuals in each group died or received LTX.

FEV1 >= −2.3 z−score, n = 119   FEV < −2.3 z−score, n = 118
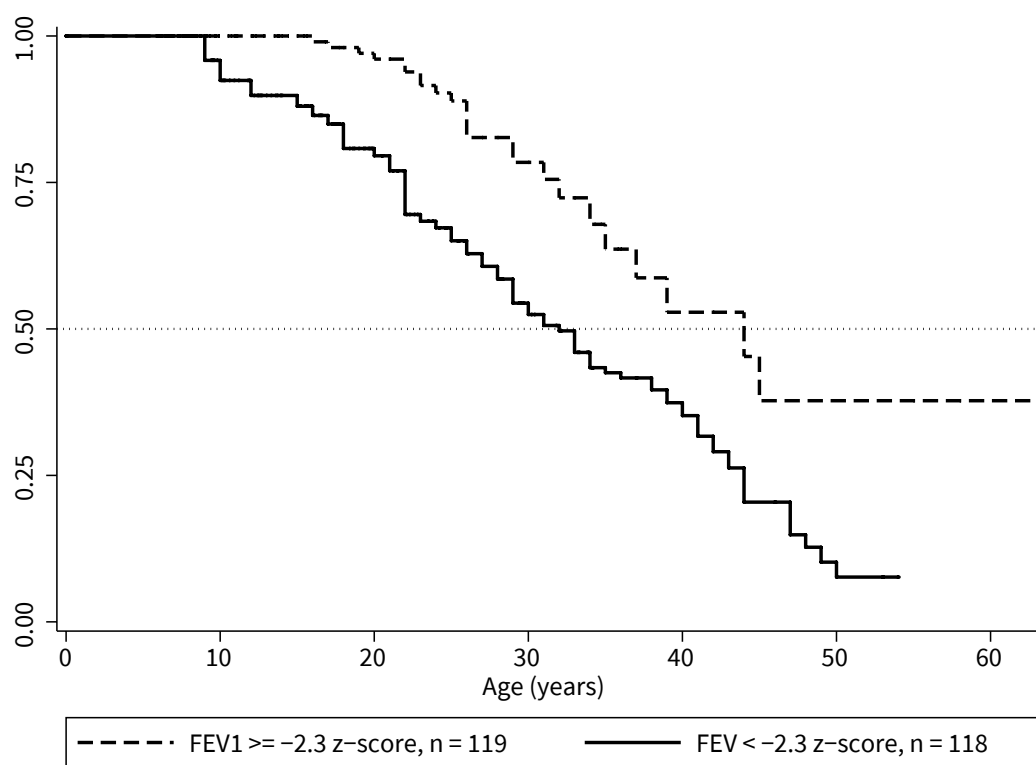
Figure S3. Respiratory survival in the sensitivity analyses. A) Individuals with ≥ 3 MBW measurements within 3 years and average baseline LCI values ≤ study population median of 8.3 z-score, n = 84 (dashed line) vs. individuals with average baseline LCI values > study population median of 8.3 z-score, n = 84 (solid line). *B)* Individuals with ≥ 3 MBW measurements within 3 years and average baseline FEV_1 values ≥ study population median of -2.3 z-score, n = 94 (dashed line) vs. adults with average baseline FEV_1 values < study population median of -2.3 z-score, n = 94 (solid line); *C)* Children (≤ 16.0 years of age) with baseline LCI value ≤ study population median of 7.2 z-score, n = 84 (dashed line) vs. children with baseline LCI value > study population median of 7.2 z-score, n = 84 (solid line); *D)* Children (≤ 16.0 years of age) with baseline FEV_1 value ≥ study population median of -1.6 z-score, n = 84 (dashed line) vs. children with baseline FEV_1 value < study population median of -1.6 z-score, n = 84 (solid line). *E)* Individuals born after 1987 with baseline LCI value ≤ study population median of 7.5 z-score, n = 51 (dashed line) vs. individuals with baseline LCI value > study population median of 7.5 z-score, n = 51 (solid line). *F)* Individuals born after 1987 with baseline FEV_1 value ≥ study population median of -1.2 z-score, n = 51 (dashed line) vs. individuals with baseline FEV_1 value < study population median of -1.2 z-score, n = 51 (solid line). CF = Cystic fibrosis, FEV_1 = Forced expired volume in the first second, LCI = Lung clearance index, LTX = Lung transplantation, p = 0.50: 50% of the individuals in each group died or received LTX.
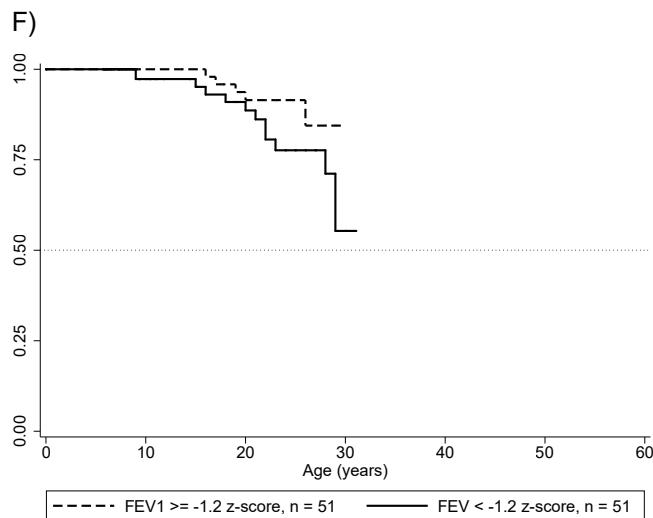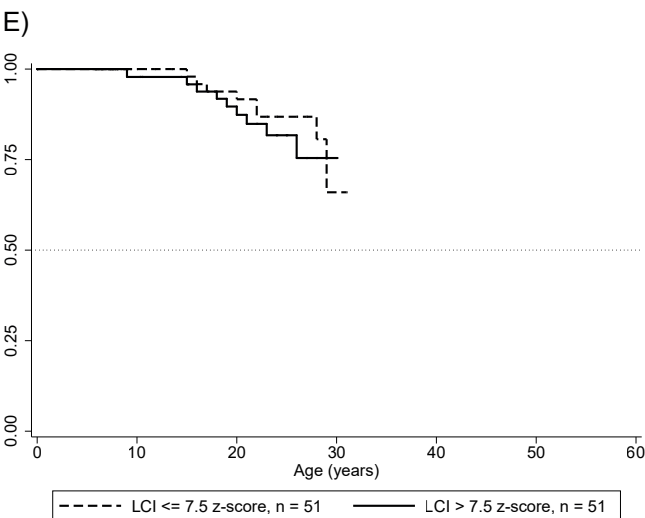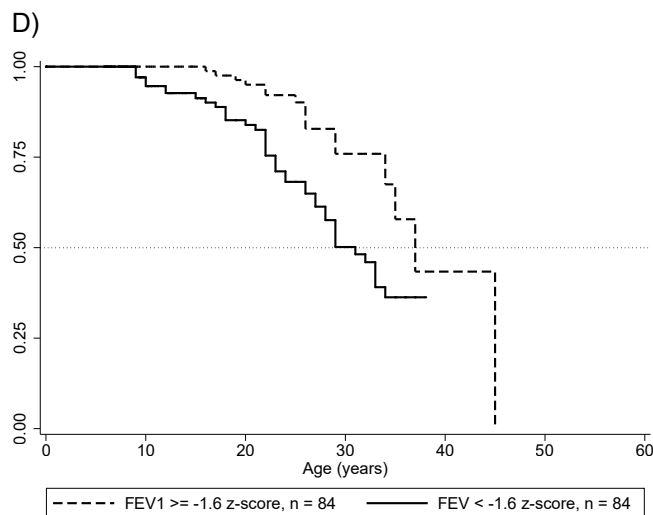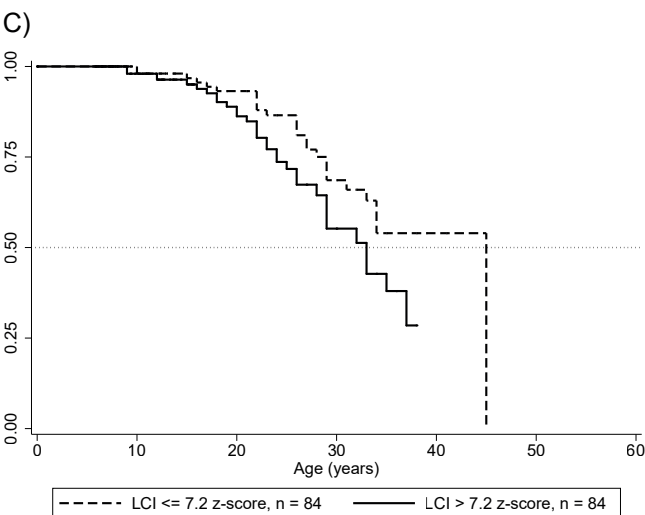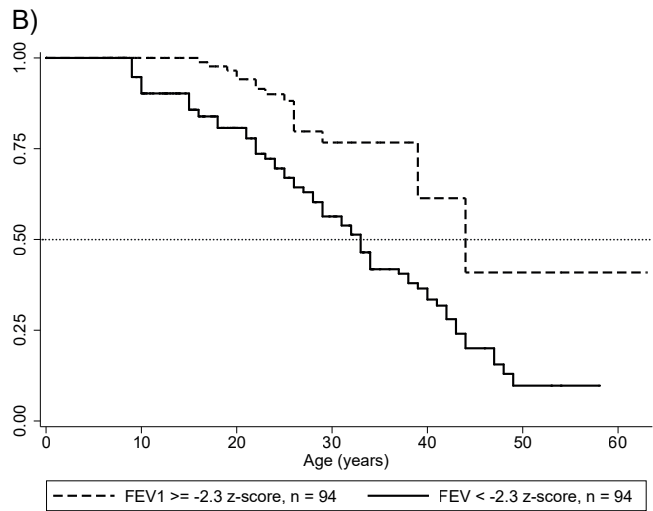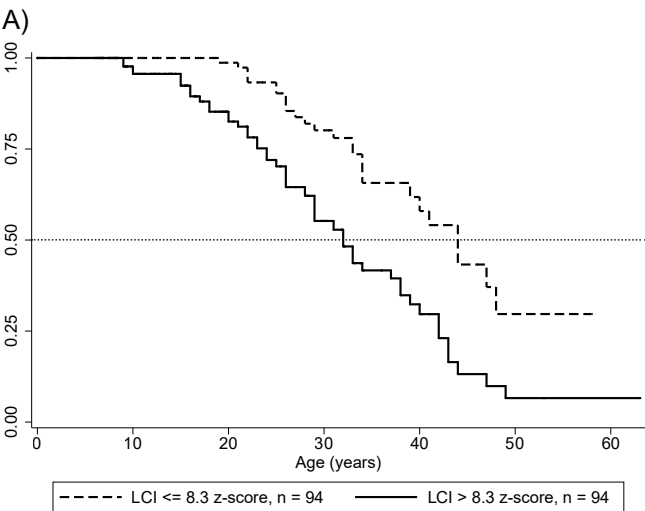
Figure S4. Directed acyclic graph (DAG) of a causal structure possibly underlying the associations of LCI and FEV₁ with survival in individuals with CF. CF influences LCI and FEV1 (dotted arrow) and also death or LTX (dashed arrow), but LCI and FEV1 are not a cause of death or LTX, therefore there is no arrow between LCI and FEV1 and death and LTX.

Surrogate measures of the exposure
LCI, FEV1

Infection, exacerbation, (…)

Exposure
Cystic Fibrosis

Outcome
Death or LTX

Confounders
Sex, age, BMI, year of birth (…)