Supplementary Appendix 1

This appendix has been provided by the authors to give readers additional information about their work.

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Patterns of Lung Function Growth and Decline in Persistent Childhood Asthma

Supplementary Appendix 1

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Part 1. Additional Figures and Tables

Figure S1: CAMP trial and continuation studies design schematic

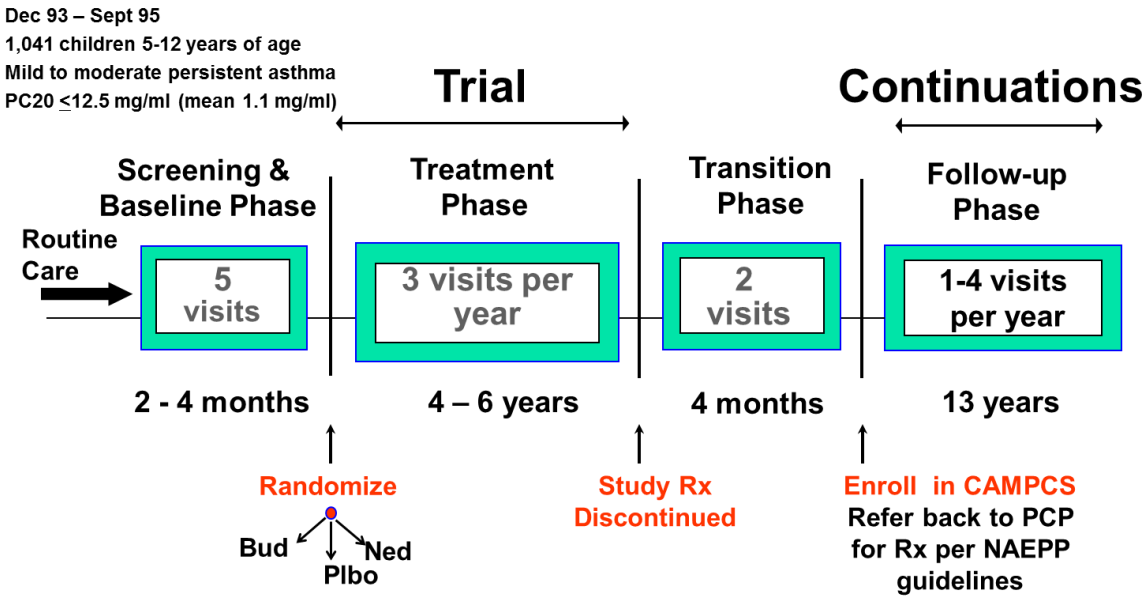
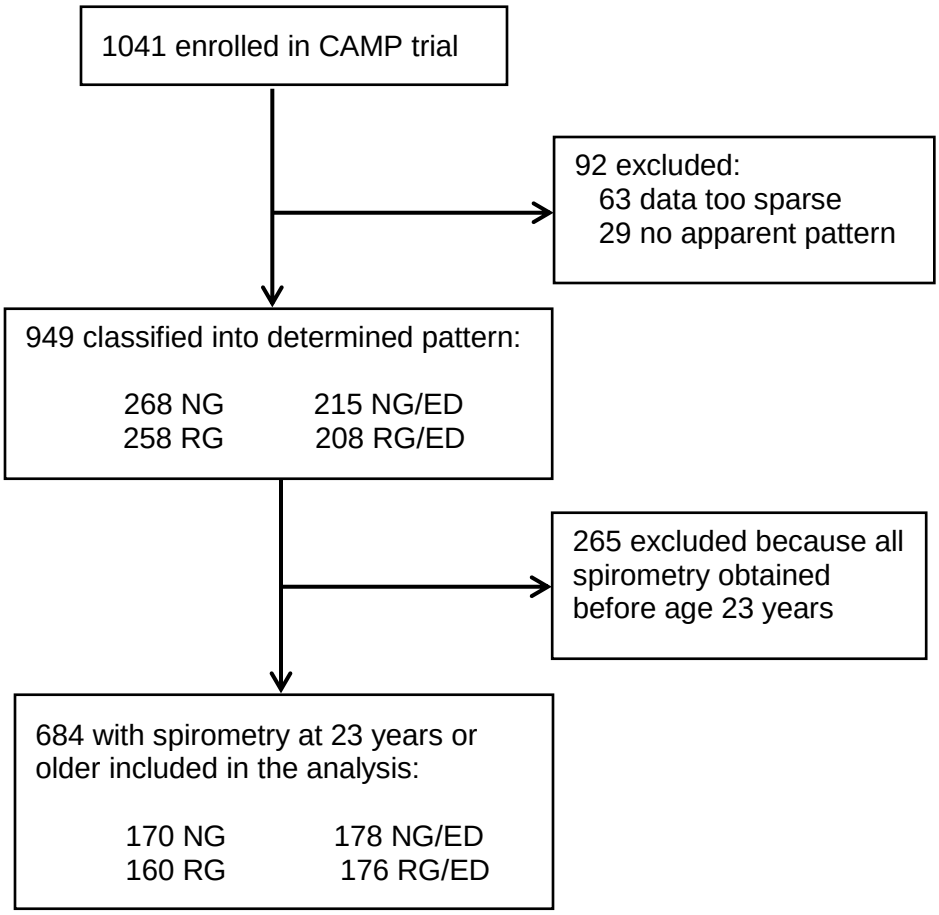
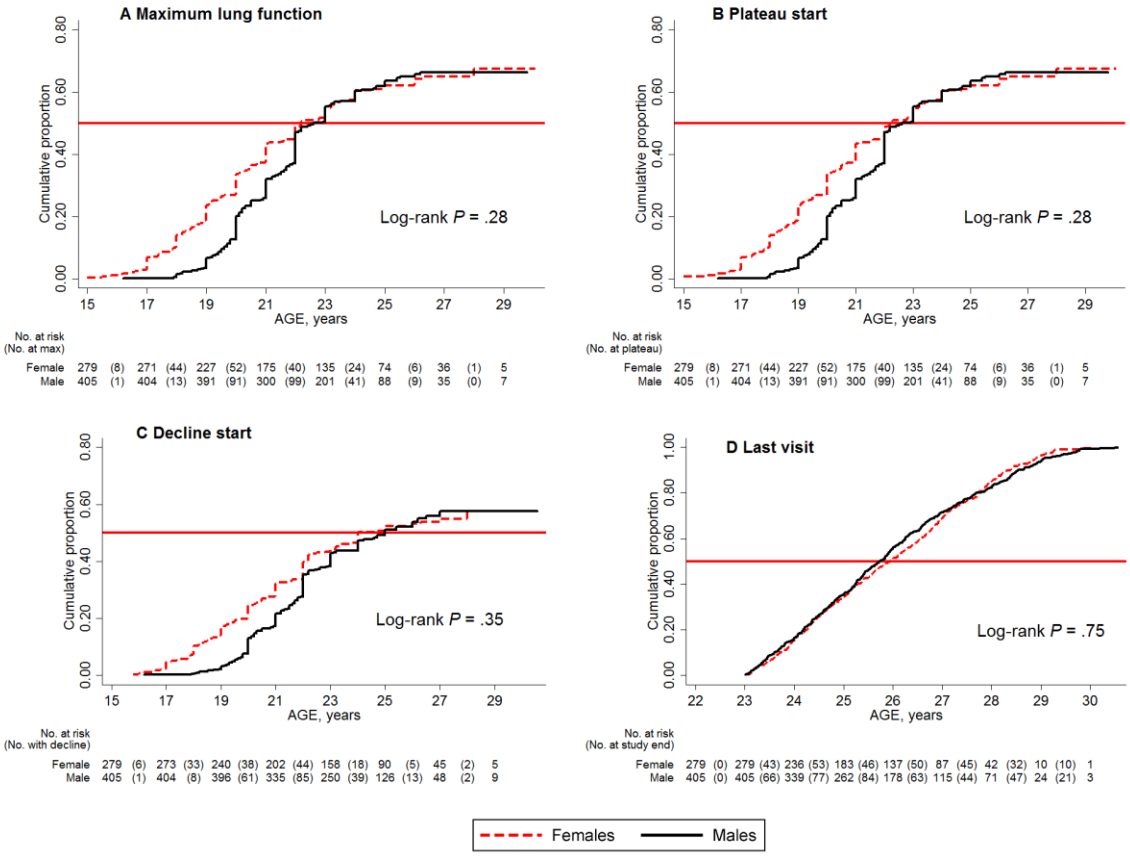


Figure S2: Derivation of the subset of CAMP participants included in pattern analyses



Abbreviations: NG denotes Normal growth, NG/ED denotes Normal growth with early decline; RG denotes Reduced growth; RG/ED denotes Reduced growth with early decline

Figure S3: Kaplan-Meier estimates of lung growth features by sex



Kaplan-Meier estimates of lung growth features by sex for the 684 CAMP participants with at least one FEV_1 measure at age 23 years or older and a determined pattern assignment. Each panel displays the cumulative proportion of participants reaching an event by age: Panel A), attainment of maximum lung function growth; Panel B), beginning the plateau phase (or maximum lung function if no plateau due to an immediate decline); Panel C), beginning the decline phase, which may or may not be earlier than expected from NHANES III; Panel D), completing their last visit in the study. The red line indicates the median age to each event. The difference between the survivorship functions is calculated by a log-rank test.

Table S1: Lung function growth pattern classification agreement between two investigators for initial pattern review

Investigator 1 Pattern Classifications	Investigator 2 Pattern Classifications*					
	No.	**NG**	**NG/ED**	**RG**	**RG/ED**	**Total**
	NG	28	0	0	0	28
	NG/ED	2	20	0	2	24
	RG	0	0	21	0	21
	RG/ED	0	1	1	26	28
	Total	30	21	22	28	101†
	Kappa	0.92				
	95% C.I.	0.86-0.98				
	***P*‡**	<0.001				

* NG denotes Normal growth, NG/ED denotes Normal growth with early decline, RG denotes Reduced growth, RG/ED denotes Reduced growth with early decline

† 110 patterns classified independently by 2 investigators; of these, 3 patterns were classified as sparse data by at least 1 investigator, and 6 were classified as unknown pattern by at least 1 investigator, which resulted in 101 patterns classified with a determined pattern by both investigators.
For the 110 patterns: Kappa=0.83, 95% C.I.: 0.76-0.91, $P<0.001$.

‡ P determined from the asymptotic test of the hypothesis that kappa equals zero.

Table S2: Lung function growth pattern classification agreement between two additional investigators of 100 CAMP participants' lung function curves

		Investigator 3 Pattern Classifications*				
Investigator 4 Pattern Classifications	**No.**	**NG**	**NG/ED**	**RG**	**RG/ED**	**Total**
	NG	36	1	0	0	37
	NG/ED	2	11	0	0	13
	RG	1	0	25	1	27
	RG/ED	0	0	3	20	23
	Total	39	12	28	21	100†
	Kappa	0.89				
	95% C.I.	0.81-0.96				
	P‡	**<0.001**				

* NG denotes Normal growth, NG/ED denotes Normal growth with early decline, RG denotes Reduced growth, RG/ED denotes Reduced growth with early decline

† 100 patterns were selected randomly from the total number of 684 participants with high-confidence patterns (i.e., participant had a determined pattern code and at least 1 spirometry at age 23 years or older) used for the analyses of pattern characteristics and predictors. Each of the 100 patterns was classified independently by 2 investigators, after an initial training period.

‡ P determined from the asymptotic test of the hypothesis that kappa equals zero.

Table S3: Lung function growth statistics by sex

	Male	**Female**	
	(N=405)	**(N=279)**	**P***
Maximum lung function:			
Attained, N (%)	254 (63%)	175 (63%)	0.99
Age at highest attained lung function, years	21.3 (1.8) [16.2, 27.8]	20.3 (2.5) [15.0-28.0]	**<0.001**
Kaplan-Meier estimated median (95% C.I.) age, years	22.7 (22.0,23.0)	22.2 (21.5,23.2)	0.28†
Plateau phase:			0.73
Not attained, N (%)	151 (37%)	104 (37%)	
No plateau, immediate decline	125 (31%)	93 (33%)	
Plateau attained, N (%)	129 (32%)	82 (29%)	
Age when attained plateau, if have a plateau, years	21.4 (1.7) [18.0,26.0]	20.6 (2.4) [15.0,26.0]	**0.002**
Kaplan-Meier estimated median (95% C.I.) age start at plateau, years	22.6 (22.0,23.0)	22.2 (21.5,23.2)	0.28†
Plateau length, if plateau phase complete:			
N (%) with a plateau	84 (21%)	53 (19%)	0.58
Length of plateau, years	1.7 (0.9) [0.8,4.5]	1.6 (0.8) [1.0, 5.2]	0.34
Decline phase: N (%)	209 (52%)	146 (52%)	0.85
Had an early decline, N (%)	209 (52%)	145 (52%)	0.89
Age at start of early decline, years	21.7 (1.9) [16.2,27.0]	20.5 (2.4) [15.8,28.0]	**<0.001**
Kaplan-Meier estimated median (95% C.I.) age at start of any decline, years	25.0 (24.0,26.5)	24.0 (23.0,.)	0.35†
Age at last visit, N (%)	25.9 (1.8) [23.0,30.6]	26.0 (1.7) [23.0,30.1]	0.66
Kaplan-Meier estimated median (95% C.I.) age, years	25.7 (25.4,26.0)	26.0 (25.6,26.3)	0.75†
* Means (SD) [minimum, maximum] estimates are presented unless otherwise denoted. P (2-sided) determined from either a Pearson's chi-square test for categorical variables or a t-test for continuous variables.			
† Median and 95% confidence interval determined from the Kaplan-Meir product-limit estimates of the survival function. P determined from the log-rank test for equality of survivor functions between genders.			

Table S4: Lung function and lung function growth statistics by 4 patterns of lung function growth and decline

	Normal Growth (N=170)	**Normal Growth/ Early Decline (N=178)**	**Reduced Growth (N=160)**	**Reduced Growth/ Early Decline (N=176)**	**Total* (N=684)**	**P†**
No. of lung function measures per participant, mean (SD) [min, max]:						
Total number	23.0 (2.8) [12, 27]	23.1 (2.8) [10,27]	22.9 (2.9) [4, 27]	23.4 (2.6) [14, 27]	23.1 (2.8) [4, 27]	0.24
Number at age 23+ years	3.1 (1.6) [1, 7]	3.3 (1.9) [1, 8]	3.1 (1.9) [1, 8]	3.6 (1.9) [1, 8]	3.3 (1.8) [1, 8]	**0.001**
Characteristics of follow-up:						
Number of years of follow-up	16.4 (0.6)	16.4 (0.7)	16.4 (0.6)	16.4 (0.7)	16.4 (0.6)	0.70
Age at randomization (years)	9.3 (1.7)	9.7 (1.7)	9.3 (1.8)	9.9 (1.7)	9.6 (1.7)	**0.006**
Age at last visit (years)	25.7 (1.7)	26.0 (1.8)	25.8 (1.9)	26.3 (1.7)	26.0 (1.8)	**0.008**
Maximum lung function attained: N (%)	45 (26%)	178 (100%)	30 (19%)	176 (100%)	429 (63%)	**<0.001**
Age at highest attained lung function, years	22.3 (2.2)	20.6 (2.2)	21.9 (1.7)	20.6 (1.8)	20.9 (2.1)	**<0.001**
Velocity from maximum to study end:						
Velocity (mL pre-BD FEV_1/yr), median [Q1, Q3]§	-0 [-22, 12)	-30 [-67, -12]	-10 [-45, 24]	-32 [-68, -15]	-28 [-62, -8]	**0.002**
Velocity (% predicted pre-BD FEV_1/yr), median [Q1, Q3]§	0.2 [-0.2, 0.9]	-0.6 [-1.4, -0.2]	0.1 [-0.7, 0.5]	-0.9 [-1.4, -0.2]	-0.5 [-1.2,-0.1]	**<0.001**
Plateau phase:						**<0.001**
Plateau not attained: maximum lung function not attained	125 (74%)	0 (0%)	130 (81%)	0 (0%)	255 (37%)	
No plateau, immediate decline	0 (0%)	112 (63%)	0 (0%)	106 (60%)	218 (32%)	
Attained plateau	45 (26%)	66 (37%)	30 (19%)	70 (40%)	211 (31%)	
Age when attained plateau, years	22.3 (2.2)	20.6 (2.1)	21.9 (1.7)	20.5 (1.6)	21.1 (2.1)	**<0.001**
Plateau phase is complete, N (%)‡¶	1 (1%)	66 (37%)	0 (0%)	70 (40%)	137 (20%)	0.60
Length of plateau if complete, years‡¶	2.0	1.5 (0.6)	--	1.8 (0.9)	1.6 (0.8)	**0.03**
For subjects attaining a plateau:						
Length of follow-up, years	16.4 (0.6)	16.3 (0.8)	16.4 (0.3)	16.4 (0.7)	16.4 (0.7)	0.44
No. spirometry measures after plateau start, mean (SD) [minimum, maximum]	4.4 (2.0) [2, 10]	5.8 (2.1) [2, 13]	4.6 (2.4) [2, 10]	6.1 (2.2) [4, 13]	5.3 (2.3) [3, 7]	**<0.001**
Time from randomization to plateau start, years	12.7 (2.3)	10.8 (2.0)	12.5 (2.3)	10.7 (2.2)	11.4 (2.3)	**<0.001**
Time from plateau start to last visit, years	3.7 (2.1)	5.4 (2.1)	3.0 (2.4)	5.7 (2.2)	4.9 (3.3)	**<0.001**
Decline phase: N (%)	1 (1%)	178 (100%)	0 (0%)	176 (100%)	355 (52%)	
Age at start of decline, years	24	21.1 (2.3)	-	21.3 (2.0)	21.2 (2.2)	0.46
Had an early decline‡¶**:** N (%)	-	178 (100%)	-	176 (100%)	354 (52%)	
Time from decline to last visit, years	-	5.0 (2.3)	--	5.0 (2.3)	5.0 (2.5)	0.76
No. spirometry measures after decline start, mean (SD) [minimum, maximum]	--	5.5 (2.5) [2, 12]	--	5.5 (2.3) [2, 12]	5.5 (2.4) [2.0, 12]	0.94
Rate of decline (mL pre-BD FEV_1/yr), mean (SD) [minimum, maximum]‖	--	-50 (54) [-295, 0]	--	-53 (59) -506, 0]	-51 (57) [-506, 0]	0.99
Rate of decline (% predicted pre-BD FEV_1/yr), mean (SD) [minimum, maximum]‖	--	-1.1 (1.2) [-6.3, 0]	--	-1.1 (1.4) [-11.6, 0]	-1.1 (1.3) [-11.6, 0]	0.79
Lung function at randomization:						
% predicted pre-BD FEV_1	100.5 (13.4)	99.7 (12.9)	87.5 (12.6)	83.8 (12.9)	93.0 (14.9)	**<0.001**
% predicted pre-BD FVC	107.7 (12.0)	107.1 (11.2)	99.6 (12.4)	96.3 (12.6)	102.7 (13.0)	**<0.001**
Pre-BD FEV_1/FVC (%)	81.9 (6.9)	81.6 (7.5)	76.5 (7.9)	76.5 (8.4)	79.2 (8.1)	**<0.001**
Bronchodilator response**(%)	8.9 (7.8)	8.2 (7.8)	12.7 (9.9)	12.4 (11.3)	10.5 (9.5)	**<0.001**
Airway responsiveness**(log mg/ml)	0.3 (1.2)	0.4 (1.1)	-0.2 (1.1)	-0.2 (1.1)	0.1 (1.2)	**<0.001**

Lung function at last follow-up visit:						
% predicted pre-BD FEV_1	104.3 (7.6)	97.7 (9.5)	87.1 (7.9)	79.7 (10.0)	92.2 (13.0)	**<0.001**
% predicted pre-BD FVC	109.9 (8.9)	105.7 (10.3)	100.6 (10.8)	94.7 (10.9)	102.7 (11.7)	**<0.001**
Pre-BD FEV_1/FVC (%)	80.4 (6.4)	78.1 (7.2)	73.0 (8.0)	71.2 (9.6)	75.7 (8.7)	**<0.001**
Post-BD FEV_1/FVC (%)	83.3 (6.1)	81.8 (6.2)	77.0 (7.6)	75.6 (8.6)	79.4 (7.9)	**<0.001**
Bronchodilator response**(%)	3.7 (2.9)	5.2 (5.4)	6.1 (4.7)	8.2 (9.1)	5.8 (6.2)	**<0.001**
Airway responsiveness**(log mg/ml)	2.4 (1.4)	2.3 (1.5)	1.7 (1.7)	1.5 (1.8)	2.0 (1.6)	**<0.001**
Have chronic airflow obstruction (pre-BD)††	11 (6%)	21 (12%)	56 (35%)	75 (41%)	163 (24%)	**<0.001**
Have chronic airflow obstruction (post-BD)‡‡	2 (1%)	9 (5%)	25 (16%)	37 (21%)	73 (11%)	**<0.001**

Number (percent of pattern) or mean (SD), unless otherwise noted.

Abbreviations: BD = bronchodilator

* Participants with a determined pattern and at least 1 spirometry measure at age 23 years or higher were included.

† P value (2-sided) for difference across pattern groups determined from either a chi-square test for non-ordered categories (categorical variables) or ANOVA (continuous variables).

‡ P value (2-sided) for difference across the 2 pattern groups with either participants attaining a plateau or having an early decline determined from either a chi-square test for non-ordered categories (categorical variables) or ANOVA (continuous variables); the data of the 1 participant with NG was excluded.

§ Rate of decline from the maximum attained lung function to study end estimated from each participant's visit spirometry measures between age at maximum lung function and end of follow-up divided by the number of years from the attainment of maximum to end of study; the smoothed curve's lung function estimates were not utilized in this estimation.

¶ 1 participant with a NG pattern was determined to have a decline; however, the decline was not earlier than expected.

‖ Rate of decline estimated from each participant's visit spirometry measures between age at start of decline and end of follow-up divided by the number of years from the start of decline to end of study; the smoothed curve's lung function estimates were not utilized in this estimation; therefore, 27 (8%) participants did not exhibit a negative rate using this method and were excluded from the averages reported. The average including all participants was: -43 (65) mL FEV_1/yr decline, 9.9 (1.5) % predicted FEV_1/yr decline, no difference between NG/ED and RG/ED.

** Bronchodilator response defined as [(post-BD FEV_1 – pre-BD FEV_1)/pre-BD FEV_1] * 100; airway responsiveness defined as the concentration of methacholine interpolated between a concentration in the nebulizer that when aerosolized caused a 20 percent decrease in FEV_1 and one that did not.

†† Chronic airflow obstruction defined as pre-BD FEV_1/FVC<0.70; using the modified definition pre-BD FEV_1/FVC<LLN (NHANES III 5^{th} percentile value): 28 (16%) of NG, 52 (29%) of NG/ED, 85 (53%) of RG, 105 (60%) of RG/ED, 270 (39%) of 684 subjects (P<0.001)

‡‡ Chronic airflow obstruction defined as post-BD FEV1/FVC<0.70 as specified by the GOLD spirometric classification criterion; using the modified GOLD criteria defined as post-BD FEV_1/FVC<LLN (NHANES III 5^{th} percentile value): 10 (6%) of NG, 19 (11%) of NG/ED, 57 (36%) of RG, 63 (36%) of RG/ED, 149 (22%) of 684 subjects (P<0.001)

Table S5: Additional baseline characteristics and end of study smoking status of participants by pattern of lung function growth and decline

	Normal Growth (N=170)	**Normal Growth/ Early Decline (N=178)**	**Reduced Growth (N=160)**	**Reduced Growth/ Early Decline (N=176)**	**P***
Pattern, %	25%	26%	23%	26%	
Trial treatment group:					0.94
Budesonide	53 (31%)	51 (29%)	45 (28%)	51 (29%)	
Nedocromil	46 (27%)	59 (33%)	50 (31%)	53 (30%)	
Placebo	71 (42%)	68 (38%)	65 (41%)	72 (41%)	
Demographic/Physical exam:					
Race/ethnicity:					**<0.001**
White non-Hispanic	125 (74%)	114 (64%)	110 (69%)	107 (61%)	
Black non-Hispanic	31 (18%)	31 (17%)	14 (9%)	17 (10%)	
Other non-Hispanic	3 (2%)	10 (6%)	17 (11%)	15 (9%)	
Hispanic	11 (6%)	23 (13%)	19 (12%)	37 (21%)	
Parent education†: College degree or higher	97 (57%)	97 (54%)	78 (49%)	87 (49%)	0.35
Income < $30,000	46 (27%)	36 (20%)	28 (18%)	34 (19%)	0.13
Age at puberty†, years	11.1 (1.4)	11.1 (1.4)	11.3 (1.5)	11.4 (1.3)	0.08
Vitamin D insufficiency (≤ 30 ng/ml) at randomization	50 (30%)	70 (40%)	59 (38%)	68 (39%)	0.15
Asthma history/Atopy/Inflammation:					
Moderate severity	79 (47%)	104 (58%)	82 (51%)	95 (54%)	0.16
Maternal history of asthma	42 (25%)	53 (30%)	52 (33%)	49 (28%)	0.36
Ever had a physician diagnosis of eczema	46 (27%)	52 (29%)	33 (21%)	31 (19%)	**0.04**
≥ 3 positive skin tests	120 (71%)	134 (75%)	116 (73%)	143 (81%)	0.11
Eosinophils ≥275 cells/μL	109 (65%)	112 (64%)	102 (65%)	122 (70%)	0.65
Serum IgE ≥ 1150 ng/ml	52 (31%)	43 (25%)	47 (30%)	55 (32%)	0.48
Sensitive and exposed to perennial allergen†	122 (72%)	132 (74%)	116 (73%)	137 (78%)	0.58
Smoking‡ exposure:					
Smoke‡ (ever)	63 (37%)	58 (33%)	57 (36%)	59 (34%)	0.82
Lifetime smoked‡ (pack-years)	0.5 (1.5)	0.4 (1.4)	0.4 (1.1)	0.5 (1.5)	0.97

Number (percent of pattern) or mean (SD).

Abbreviations: IgE=immunoglobulin E

* P value (2-sided) for difference across pattern groups determined from either a chi-square test for non-ordered categories (categorical variables) or ANOVA (continuous variables).

† Parent education denotes the highest level reached by either parent; age at puberty defined as the year of age when at least 1 Tanner component (pubic hair and either breast for girls or genital stage for boys) greater than Stage 1; perennial allergens include dog, cat, cockroach, mite, mold.

‡ Cigarette smoking only; smoking and amount determined through the end of follow-up

Table S6: Relative odds of completing spirometric testing at age 23 years or older in relation to baseline characteristics

	Completers vs. Non-completers*		
Baseline characteristics	**O.R.†**	**95% C.I.†**	**P†**
Sex: male vs. female	0.98	0.73-1.32	0.90
Age at randomization (years)	**1.69**	**1.53-1.87**	**<0.001**
Race/ethnicity:			0.57
White Non-Hispanic	1.00		
Non-Hispanic Black	1.17	0.73-1.87	0.51
Any Hispanic	1.26	0.77-2.06	0.36
Asthma severity: moderate vs. mild	0.93	0.69-1.27	0.66
Duration since asthma diagnosis:			0.89
Medium (< 3 years)	1.00		
Short (3-6 years)	0.93	0.65-1.31	0.67
Long (≥7 years)	1.02	0.67-1.56	0.93
Tanner stage 1 (vs. stage 2-5)‡	**1.77**	**1.16-2.70**	**0.008**
≥ 3 positive skin tests (yes vs. no)	1.16	0.75-1.78	0.51
Assigned treatment group:			0.51
Budesonide vs. Placebo	0.87	0.62-1.23	0.44
Nedocromil vs. Placebo	1.09	0.76-1.54	0.65

* Completer defined as a participant having at least one spirometric measure at age 23 years or older and a defined lung function growth pattern. A non-completer is defined as a participant with insufficient longitudinal spirometric data or having a lung function growth pattern that is not defined by one of the 4 growth pattern groups.

† OR (odds ratios), 95% C. I. (confidence interval), and P values derived from multiple logistic regression analyses comparing baseline characteristics in relation to completers versus non-completers. All covariates listed in the table were included in the model; additionally the model also included indicator variables for clinic.

‡ Tanner stage 1 defined as pre-pubertal, i.e., no Tanner components (pubic hair and either breast for girls or genital stage for boys) greater than Stage 1.

Note: Of the 1041 participants randomized into the CAMP trial, data for a total of 1036 (99.5%) participants were included in the logistic regression distributed as follows: 681 in completer group and 355 in the non-completer group. Missing data in 1 or more of the predictors excluded 5 participants from inclusion in the regression.

Table S7: Multinomial regression of demographic and clinical risk factors of 4 patterns of lung function growth and decline: results for all predictors in the model

	NG/ED vs. NG **Normal Growth/Early Decline vs. Normal Growth**				**RG vs. NG** **Reduced Growth vs. Normal Growth**				**RG/ED vs. NG** **Reduced Growth/Early Decline vs. Normal Growth**			
	OR	**95% C.I.**		**P***	**OR**	**95% C.I.**		**P***	**OR**	**95% C.I.**		**P***
BASELINE:												
Lung function												
Pre-BD FEV_1 % predicted	1.00	0.97	1.03	0.90	0.86	0.83	0.90	**<0.001**	0.85	0.82	0.88	**<0.001**
Bronchodilator response† (%)	1.01	0.97	1.06	0.60	0.91	0.87	0.96	**<0.001**	0.91	0.87	0.95	**<0.001**
Airway responsiveness† (log_e(mg/ml))	1.03	0.79	1.34	0.83	0.61	0.44	0.84	**<0.001**	0.66	0.49	0.89	**0.008**
Demographic:												
Sex: Male vs. female	1.40	0.82	2.39	0.22	8.18	4.14	16.16	**<0.001**	3.07	1.65	5.68	**<0.001**
Age (yrs)	1.06	0.86	1.31	0.58	0.55	0.43	0.70	**<0.001**	0.62	0.49	0.80	**<0.001**
Race: White Non-Hispanic	1.00			0.86	1.00			0.25	1.00			0.42
Non-Hispanic Black	1.07	0.49	2.36	0.86	0.44	0.16	1.22	0.12	0.57	0.21	1.54	0.27
Any Hispanic	1.19	0.44	3.25	0.73	1.14	0.37	3.50	0.82	1.27	0.45	3.55	0.65
Income: < $30,000 vs. ≥$30,000	0.55	0.28	1.09	0.09	0.54	0.24	1.22	0.14	0.74	0.34	1.58	0.43
Highest parent education†: college degree or higher vs. some college or less	0.70	0.39	1.27	0.24	0.33	0.17	0.66	**0.002**	0.43	0.22	0.83	**0.01**
Asthma:												
Severity: moderate vs. mild	1.72	0.99	3.01	0.06	0.79	0.41	1.55	0.50	0.79	0.41	1.49	0.46
Duration since diagnosis:				0.89				0.65				0.31
Medium (< 3 yrs)	1.00				1.00				1.00			
Short (3 - 6 yrs)	0.99	0.53	1.84	0.97	0.83	0.40	1.74	0.63	0.84	0.41	1.75	0.65
Long (≥ 7 yrs)	1.17	0.60	2.27	0.65	1.27	0.59	2.76	0.54	1.61	0.77	3.37	0.21
Maternal history of asthma (yes vs. no)	1.21	0.67	2.19	0.54	1.90	0.96	3.77	0.07	1.08	0.56	2.11	0.82
Physical:												
BMI Z-score	1.39	1.07	1.82	**0.02**	0.81	0.60	1.09	0.17	1.02	0.76	1.36	0.89
Age at puberty† (yrs)	1.08	0.88	1.32	0.45	1.19	0.93	1.52	0.16	1.21	0.95	1.54	0.13
Vitamin D (≤30 vs. >30 ng/ml)	1.35	0.76	2.41	0.31	2.15	1.10	4.23	**0.03**	1.64	0.85	3.14	0.14
Atopy/Inflammation:												
3+ positive skin test vs. <3	1.21	0.62	2.34	0.58	1.18	0.54	2.60	0.67	2.42	1.09	5.33	**0.03**
Eczema (ever physician diagnosis; yes vs. no)	1.01	0.56	1.84	0.96	0.90	0.43	1.89	0.79	0.69	0.34	1.43	0.32
Serum IgE: ≥ 1150 vs. <1150 ng/ml	0.61	0.33	1.11	0.11	0.64	0.32	1.28	0.21	0.75	0.39	1.45	0.39
Eosinophils: ≥275 vs. <275 cells/μL	1.06	0.59	1.92	0.84	0.54	0.27	1.09	0.09	0.64	0.32	1.26	0.20
Exposures:												
Maternal smoking during	2.33	1.03	5.26	**0.04**	1.09	0.41	2.89	0.87	2.22	0.89	5.51	0.09

gestation‡ (yes vs. no)														
Sensitive and exposed to perennial allergen† (yes vs. no)	0.98	0.52	1.83	0.94		0.99	0.47	2.10	0.98		0.86	0.41	1.78	0.68
Assigned trial treatment group:				0.40					0.44					0.90
Budesonide vs. Placebo	0.78	0.42	1.44	0.42		0.63	0.30	1.31	0.22		0.85	0.42	1.73	0.66
Nedocromil vs. Placebo	1.22	0.66	2.26	0.52		0.74	0.36	1.52	0.42		0.96	0.48	1.92	0.91
Treatment 6 months before randomization:														
Inhaled corticosteroid(days/wk)	1.00	0.89	1.11	0.95		1.11	0.99	1.25	0.07		1.10	0.98	1.23	0.11
No. days on prednisone	1.04	0.99	1.10	0.15		0.99	0.93	1.06	0.86		1.00	0.94	1.07	0.99
Morbidity year before randomization:														
Urgent care visits due to asthma (No.)	1.00	1.00	1.00	0.09		1.00	1.00	1.00	0.27		1.00	1.00	1.00	0.24
Hospitalizations due to asthma (any vs none)	1.23	0.37	4.09	0.74		1.71	0.49	6.01	0.40		0.61	0.16	2.41	0.49
Use of albuterol for symptoms (puffs/wk)	0.99	0.96	1.03	0.79		1.00	0.97	1.04	0.98		1.00	0.97	1.04	0.98
FOLLOW-UP:														
Treatment through end of trial or age 18:														
Mean ICS dose/yr through end of trial	1.01	0.99	1.03	0.41		1.01	0.99	1.03	0.41		1.01	0.99	1.03	0.22
No. prednisone courses/year through trial	0.60	0.18	2.00	0.41		0.65	0.18	2.31	0.50		0.62	0.18	2.09	0.44
No. prednisone courses/year from trial end to age 18	1.15	0.37	3.55	0.81		4.12	1.14	14.91	**0.03**		2.73	0.82	9.06	0.10
Morbidity (through trial):														
Urgent care visits (no./PY)	1.00	0.99	1.01	0.52		1.00	0.99	1.01	0.78		1.00	0.99	1.01	0.65
Hospitalizations (any)	0.49	0.17	1.43	0.19		0.36	0.11	1.16	0.09		0.26	0.08	0.81	**0.02**
Episode free days† (%)	1.01	1.00	1.03	**0.03**		1.01	0.99	1.02	0.27		1.00	0.99	1.02	0.71
Exposure (through end of follow-up)														
Smoked 100 or more cigarettes by age 18‡ (yes vs. no)	0.71	0.33	1.56	0.40		1.17	0.48	2.85	0.73		0.53	0.21	1.31	0.17

Abbreviations: BD=bronchodilator; rz=randomization; BMI=body mass index; IgE=immunoglobulin E; ICS=inhaled corticosteroids

* Multinomial model conditional odds ratios (OR), 95% confidence limits (C.I.), and P values derived from multinomial regression analysis comparing NG/ED, RG, RG/ED to NG. All covariates listed in the table were included in the model; 7 indicator variables to account for the fixed effects of clinical site were also included in the model. Of the 684 participants with spirometry at age 23 or older, 614 (90%) had complete data on all variables and are included in the table. The 614 subjects were distributed among the groups as: 162 (26%) in NG/ED, 138 (22%) in RG, 158 (26%) in RG/ED, and 156 (25%) in NG.

† Bronchodilator response defined as [(post-BD FEV_1 – pre-BD FEV_1)/pre-BD FEV_1] * 100; airway responsiveness defined as the concentration of methacholine that caused a 20 percent decrease in FEV_1; highest parent education denotes the highest level reached by either parent; age at puberty defined as the year of age when at least 1 Tanner component (pubic hair and either breast for girls or genital stage for boys) was greater than Stage 1; perennial allergens include dog, cat, cockroach, mite, mold; episode free day defined as a day with no night awakenings, morning and evening peak flow ≥80 percent of personal best peak flow, no use of albuterol for symptoms, no use of prednisone, no absence from school or contact with a physician because of asthma symptoms, and no episode of wheezing, coughing, chest tightness, or shortness of breath.

‡ Cigarette smoking only

Part 2. Pattern Classification Procedures Protocol and coding sheets

Part 2A. CAMP Pattern Classification Procedures Protocol

CAMP Procedure for Lung Growth and Decline Pattern Classification

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Materials: Each expert pulmonologist was provided with a hard copy book of printouts, one page for each CAMP participant; each page contained the smoothed pre-bronchodilator FEV_1 spirometry plot by age, raw data points, and the NHANES III 50th, 25th, 10th, and 5th percentile curves for someone of that sex, age, race/ethnicity and height for one participant (see Figure 1). Participants were identified with a new random ID number developed for grading (i.e., not their standard CAMP patient ID number). All
data through March 1, 2012 were used to calculate these curves. There are no duplicate subjects in this set of 1,041. The order of the subjects is by random ID; the ID number assigned is neither the CAMP subject
ID nor the ID used for the subject if they were in the 443 (November 2009) or 563 (October 2010) pattern
sets.

Instructions: Each curve should first be classified into one of the four distinct patterns, if possible, using the smoothed curve (NOT the data points) in relation to the NHANES III reference curves. Then, determination of whether maximum growth has been attained, and whether there is a plateau or an earlier than expected decline. As a reminder, the overall pattern classification should be based on a gestalt assessment using the NHANES III reference curves as rough guidelines as below:

1. Classification of each participant as NG or RG:
   - Normal growth (NG) defined as almost always above the 25th percentile (see Example 2A, ID=1004).
   - Reduced growth (RG) defined as almost always below the 25th percentile (see Example 2B, ID=1006).

2. Classification of each participant as ED or No ED:
   - Early decline (ED) is defined as the curve rises, may plateau, and then decreases at an earlier age than expected when compared to NHANES III percentile curves.
   - No early decline is defined as any decrease in the curve following the "expected" pattern of lung function from the NHANES III 50th percentile reference curve (See Examples 2C and 2D, ID=1014 (NG/ED) and ID=1005 (RG/ED), respectively).
   - CAUTION: A data point at the very end of the curve may cause the pattern to appear to have a decline or uptick; but this may be spurious due to the influence of the last point (see Examples 2E, 2F, and 2G, IDs=1172, 1632, 1228, respectively).
   - The height of the NHANES III percentile reference curve is not used to determine whether "decline" has occurred. The *height* of the smoothed curve helps to determine whether the pattern is normal or reduced. Use the "expected" *pattern* from the lung function growth 50th percentile reference curve to determine whether the decline has occurred *earlier* than expected. Example 2H, ID=1956, displays a NG pattern with a decline, in which the decline occurs at the age expected; therefore, the pattern is coded as NG without early decline (Pattern code 1).

3. Coding of the "undetermined":

- If there is enough data to determine a pattern but the pattern does not fit in any of the 4 categories, then this pattern should be coded as "(9) Undetermined Pattern" (see Example 3A, ID=1056).
- If there is NOT enough data to determine a pattern, then code this as "(8) Sparse data" – the last choice of the pattern choices (see Examples 3B and 3C, IDs=1038, 1481, respectively).

4. Determination of maximal lung function, start of plateau, and start of decline.
   -These 3 events are to be determined independent of accompanying NHANES III percentile curves; the age at which each phase begins and if the phase has occurred should be based on the participant's individual smoothed pattern.
   -Determine whether maximum lung function growth has been attained. There is a checkbox for this on the form (see Examples 4A and 4B, ID=1140 for NG not reaching maximum lung function, ID=1018 for NG reaching maximum lung function). When maximum lung function growth occurs at the last collection of data so that it cannot be determined whether the curve will continue to rise, then check choice "No."
   -There are also checkboxes for whether the plateau phase has begun (i.e., the smoothed lung function curve levels off after reaching maximum lung function") or there is no plateau (i.e., the smoothed lung function curve does not reach maximum lung growth, but continues to rise) (see Example 4C, ID=1441 for RG with a plateau).
   -If the decline phase begins immediately after the maximum lung function is attained, then check "No plateau", "yes" decline started, and code age at plateau as "99" (see Example 4D, ID=1907 for NG/ED with no plateau and immediate decline).
   -If a phase has not begun, then code the corresponding age question for that phase as "99" (see Example 4E, ID=1759 for RG without reaching maximum lung function, a plateau start or a decline).
   -The age of attained maximum lung function and the age at the start of the plateau (if there is a plateau) must be the same. Write the age in years on the appropriate age line.
   -The age in years at which decline begins should be noted. If a decline has not started, then code age at decline as "99".

Procedure:

1. The 2 pulmonologists should BOTH classify the FIRST 50 patterns.
2. The 2 pulmonologists should SCAN and e-mail (or mail) the first 50 pages to DCC. The scanned coded sheets should be sent prior to the date of the teleconference to assess agreement between the independent coding of the first set of patterns.
3. The 2 pulmonologists should teleconference to compare classifications; DCC's representation is optional, but suggested, on this call.
4. Depending on their gestalt on the degree of agreement on the classifications, the 2 pulmonologists can each classify an additional 30 - 50 patterns, then SCAN and e-mail forms to DCC, and teleconference to compare results.
5. Once the 2 pulmonologists are satisfied that high agreement has occurred, then ONLY the first pulmonologist will classify the remaining patterns.
6. When the first pulmonologist is finished classifying the remaining patterns, he should SCAN the pages (in sets) and email to the DCC for data entry and analysis.

Adjudication of patterns the first pulmonologist could not grade conclusively:

1. The first pulmonologist sends the pattern ID number to DCC and to the second pulmonologist for a determination.
2. Results are shared after determination and patterns for which a conclusive grading was not met are discussed by the 2 pulmonologists and the DCC statistician; the first pulmonologist will make the final determination for that pattern.
3. The goal is to keep this set of patterns small; the first pulmonologist should attempt to make the grading based on his best judgment as much as possible.

Example 1A: Pattern Classification Form

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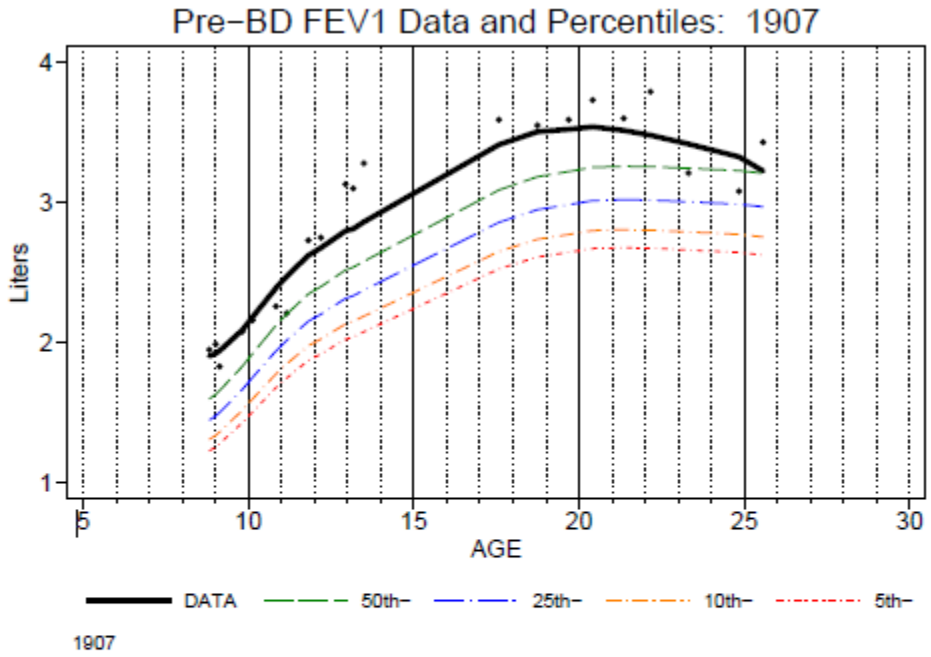

PATTERN OF GROWTH/DECLINE (Check One)
(1) Normal Growth
(2) Normal Growth, Early Decline
(3) Reduced Growth
(4) Reduced Growth, Early Decline
(9) Undetermined Pattern
(8) Undetermined - not enough data

Maximum lung growth attained: (1) Yes (0) No
Plateau started: (2) No plateau (1) Yes (0) No
Decline started: (1) Yes (0) No

AGE AT each of the following periods (use '99' if N/A):

Maximum Lung Growth: ___ ___ . ___

Start of Plateau: ___ ___ . ___

Start of Decline: ___ ___ . ___

Example 1B: Coded Pattern Classification Form

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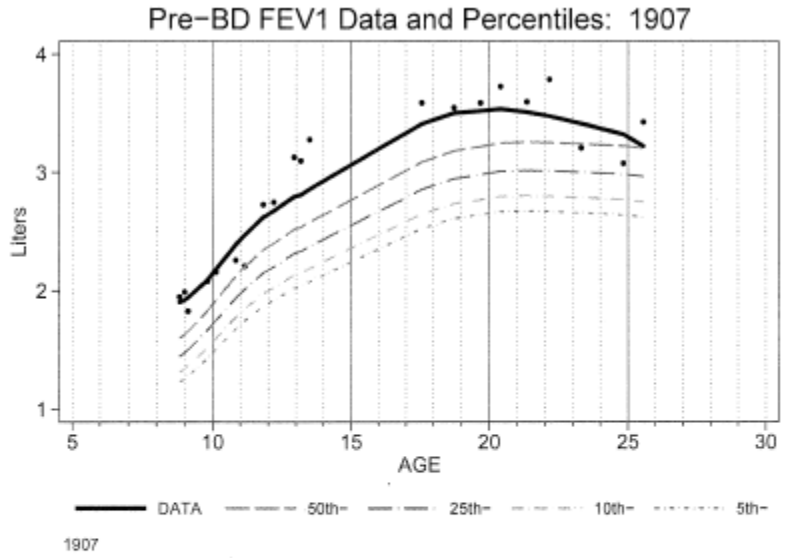

PATTERN OF GROWTH/DECLINE (Check One)
(1) Normal Growth
(✓2) Normal Growth, Early Decline
(3) Reduced Growth
(4) Reduced Growth, Early Decline
(9) Undetermined Pattern
(8) Undetermined - not enough data

Maximum lung growth attained: (✓1) Yes (0) No
Plateau started: (✓2) No plateau (1) Yes (0) No
Decline started: (✓1) Yes (0) No

AGE AT each of the following periods (use '99' if N/A):

Maximum Lung Growth: 20.3
Start of Plateau: 99.
Start of Decline: 20.3

Example 2A: Normal Growth

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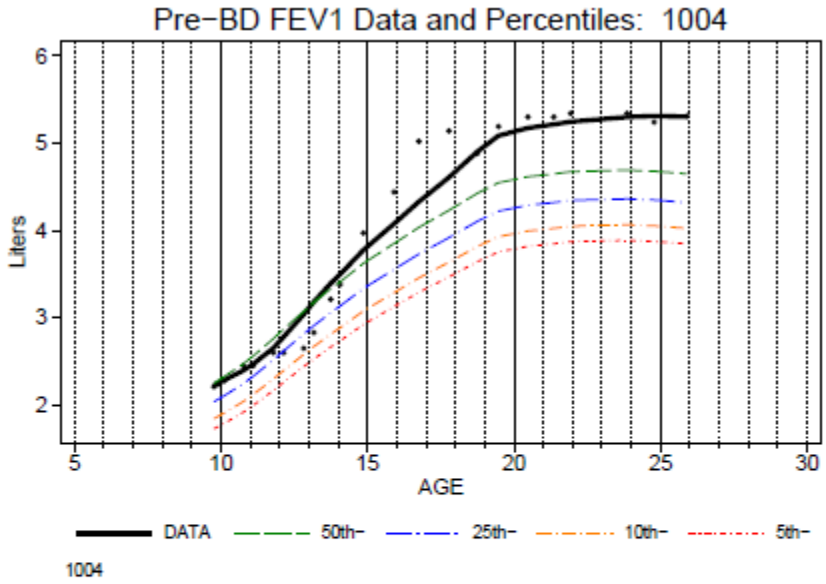


PATTERN OF GROWTH/DECLINE (Check One)
(1) Normal Growth
(2) Normal Growth, Early Decline
(3) Reduced Growth
(4) Reduced Growth, Early Decline
(9) Undetermined Pattern
(8) Undetermined - not enough data

Maximum lung growth attained: (1) Yes (0) No
Plateau started: (2) No plateau (1) Yes (0) No
Decline started: (1) Yes (0) No

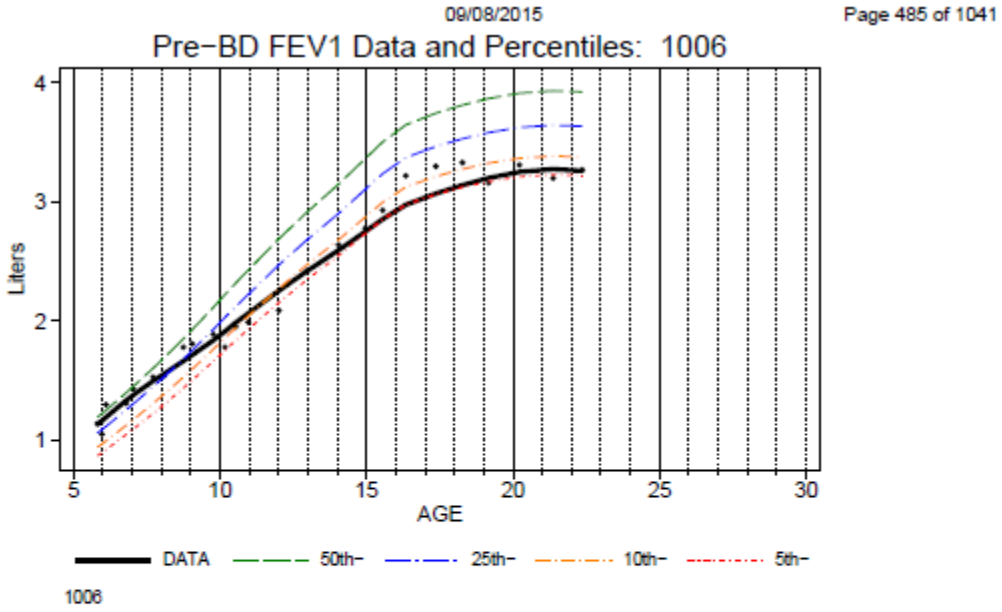
AGE AT each of the following periods (use '99' if N/A):

Maximum Lung Growth: ___ ___ . ___

Start of Plateau: ___ ___ . ___

Start of Decline: ___ ___ . ___

Example 2B: Reduced Growth



PATTERN OF GROWTH/DECLINE (Check One)
(1) Normal Growth
(2) Normal Growth, Early Decline
(3) Reduced Growth
(4) Reduced Growth, Early Decline
(9) Undetermined Pattern
(8) Undetermined - not enough data

Maximum lung growth attained: (1) Yes (0) No
Plateau started: (2) No plateau (1) Yes (0) No
Decline started: (1) Yes (0) No

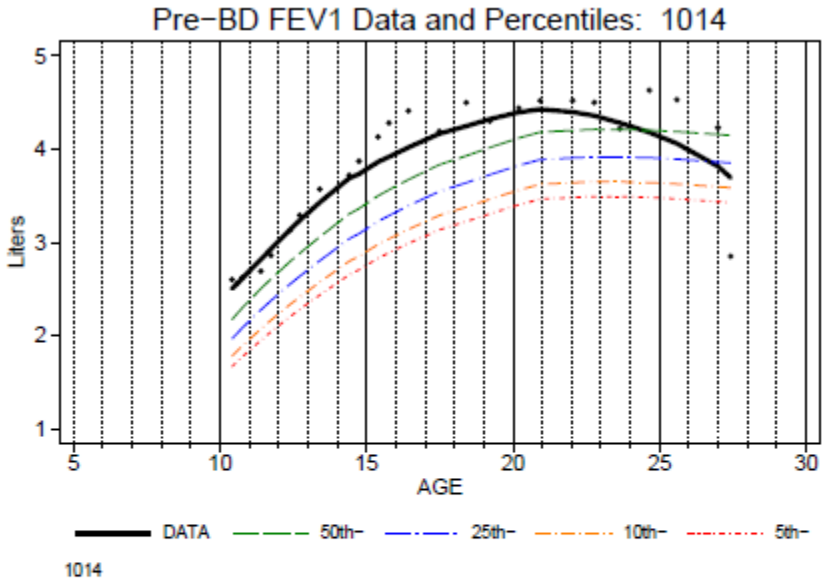
AGE AT each of the following periods (use '99' if N/A):

Maximum Lung Growth: ___ ___ - ___

Start of Plateau: ___ ___ - ___

Start of Decline: ___ ___ - ___

Example 2C: Normal Growth with Early Decline



PATTERN OF GROWTH/DECLINE (Check One)
(1) Normal Growth
(2) Normal Growth, Early Decline
(3) Reduced Growth
(4) Reduced Growth, Early Decline
(9) Undetermined Pattern
(8) Undetermined - not enough data

Maximum lung growth attained: (1) Yes (0) No
Plateau started: (2) No plateau (1) Yes (0) No
Decline started: (1) Yes (0) No

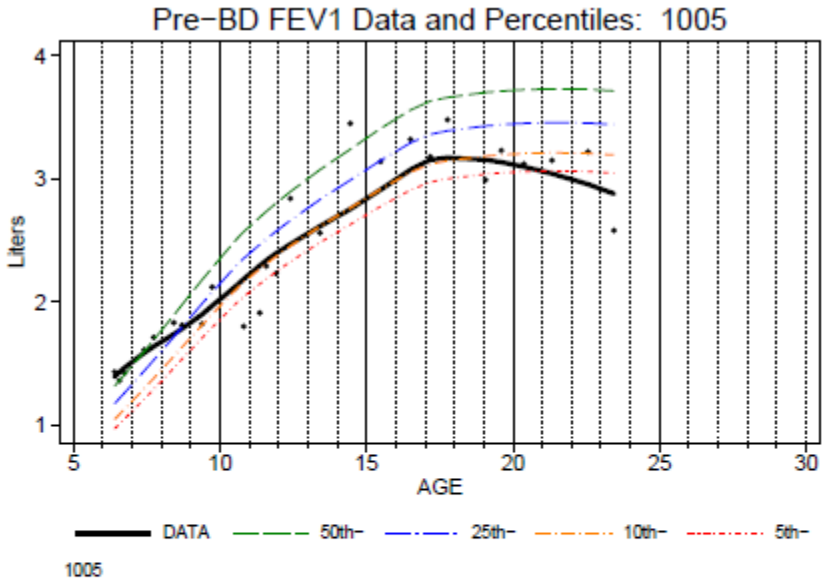
AGE AT each of the following periods (use '99' if N/A):

Maximum Lung Growth: ___ ___ . ___

Start of Plateau: ___ ___ . ___

Start of Decline: ___ ___ . ___

Example 2D: Reduced Growth with Early Decline



PATTERN OF GROWTH/DECLINE (Check One)
(1) Normal Growth
(2) Normal Growth, Early Decline
(3) Reduced Growth
(4) Reduced Growth, Early Decline
(9) Undetermined Pattern
(8) Undetermined - not enough data

Maximum lung growth attained: (1) Yes (0) No
Plateau started: (2) No plateau (1) Yes (0) No
Decline started: (1) Yes (0) No

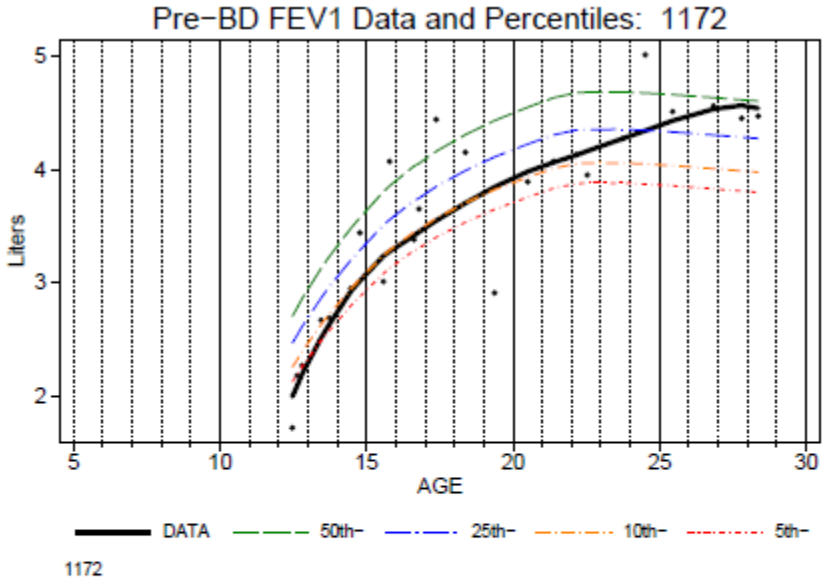
AGE AT each of the following periods (use '99' if N/A):

Maximum Lung Growth: ___ ___ . ___

Start of Plateau: ___ ___ . ___

Start of Decline: ___ ___ . ___

Example 2E: RG - not enough data points to determine plateau or decline



PATTERN OF GROWTH/DECLINE (Check One)
(1) Normal Growth
(2) Normal Growth, Early Decline
(3) Reduced Growth
(4) Reduced Growth, Early Decline
(9) Undetermined Pattern
(8) Undetermined - not enough data

Maximum lung growth attained: (1) Yes (0) No
Plateau started: (2) No plateau (1) Yes (0) No
Decline started: (1) Yes (0) No

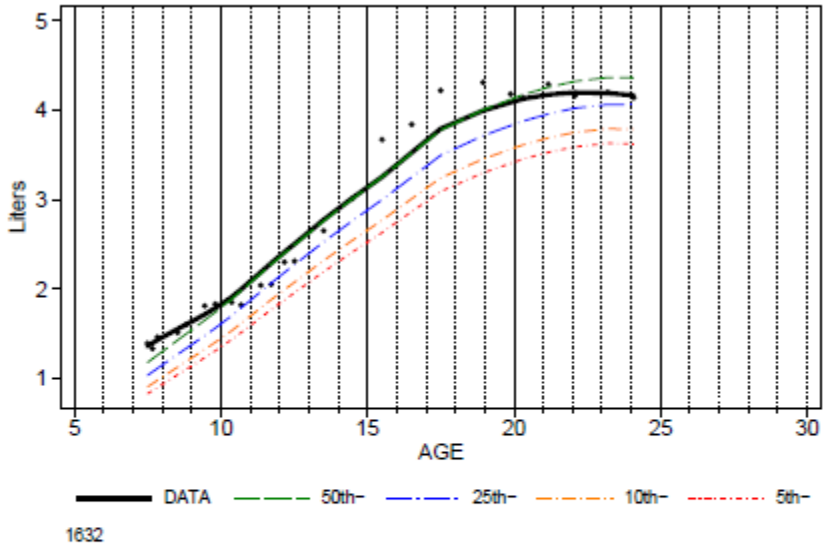
AGE AT each of the following periods (use '99' if N/A):

Maximum Lung Growth: ___ ___ . ___

Start of Plateau: ___ ___ . ___

Start of Decline: ___ ___ . ___

Example 2F: NG/ED - adequate number of data points to determine decline



PATTERN OF GROWTH/DECLINE (Check One)
(1) Normal Growth
(2) Normal Growth, Early Decline
(3) Reduced Growth
(4) Reduced Growth, Early Decline
(9) Undetermined Pattern
(8) Undetermined - not enough data

Maximum lung growth attained: (1) Yes (0) No
Plateau started: (2) No plateau (1) Yes (0) No
Decline started: (1) Yes (0) No

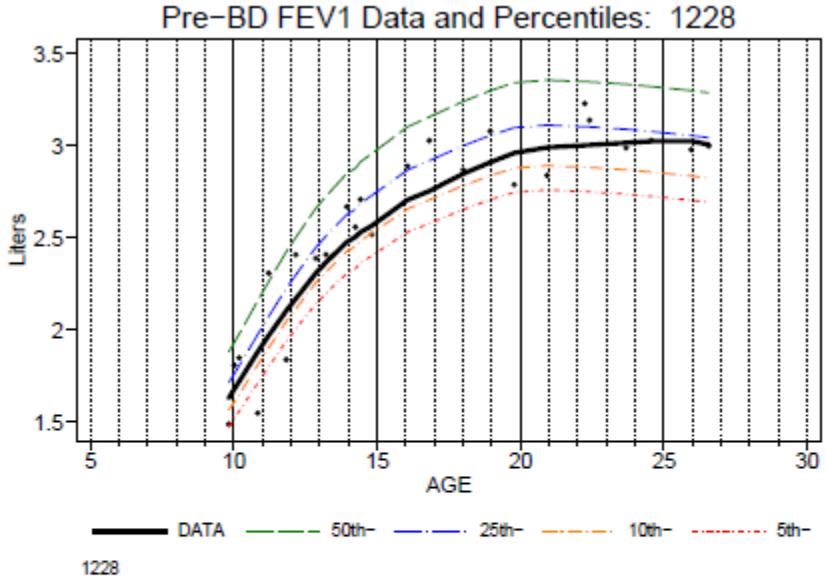
AGE AT each of the following periods (use '99' if N/A):

Maximum Lung Growth: ___ ___ . ___

Start of Plateau: ___ ___ . ___

Start of Decline: ___ ___ . ___

Example 2G: RG - not enough data points to determine plateau or decline



PATTERN OF GROWTH/DECLINE (Check One)

(1) Normal Growth
(2) Normal Growth, Early Decline
(3) Reduced Growth
(4) Reduced Growth, Early Decline
(9) Undetermined Pattern
(8) Undetermined - not enough data

Maximum lung growth attained: (1) Yes (0) No
Plateau started: (2) No plateau (1) Yes (0) No
Decline started: (1) Yes (0) No

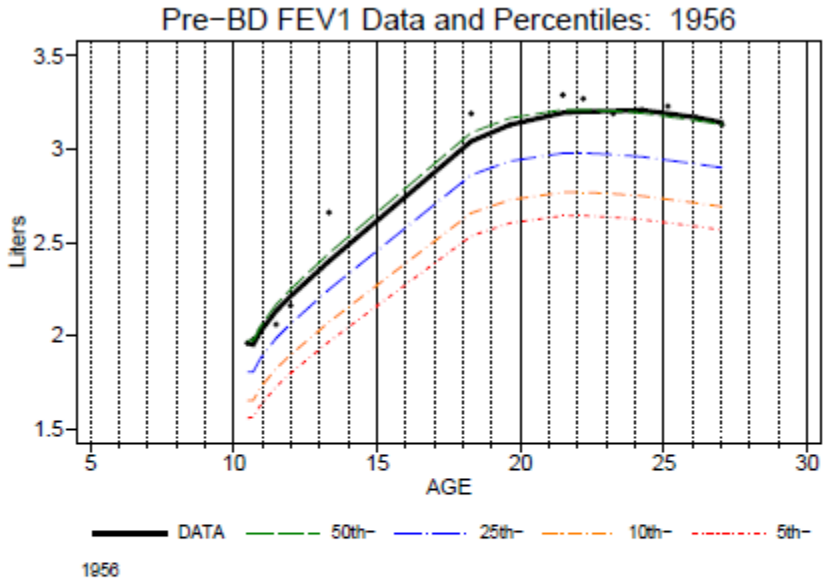
AGE AT each of the following periods (use '99' if N/A):

Maximum Lung Growth: ___ ___ . ___

Start of Plateau: ___ ___ . ___

Start of Decline: ___ ___ . ___

Example 2H: NG with decline occurring at expected age



PATTERN OF GROWTH/DECLINE (Check One)
(1) Normal Growth
(2) Normal Growth, Early Decline
(3) Reduced Growth
(4) Reduced Growth, Early Decline
(9) Undetermined Pattern
(8) Undetermined - not enough data

Maximum lung growth attained: (1) Yes (0) No
Plateau started: (2) No plateau (1) Yes (0) No
Decline started: (1) Yes (0) No

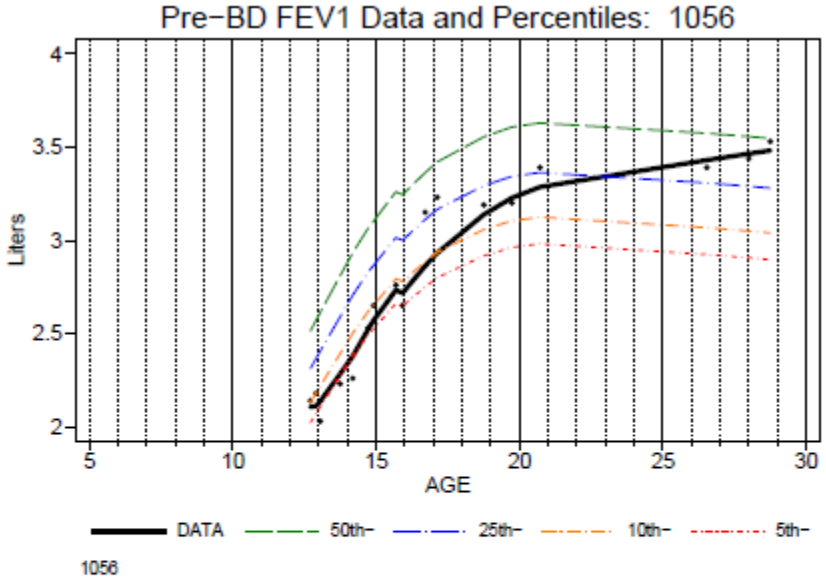
AGE AT each of the following periods (use '99' if N/A):

Maximum Lung Growth: ___ ___ . ___

Start of Plateau: ___ ___ . ___

Start of Decline: ___ ___ . ___

Example 3A: Undetermined



PATTERN OF GROWTH/DECLINE (Check One)
(1) Normal Growth
(2) Normal Growth, Early Decline
(3) Reduced Growth
(4) Reduced Growth, Early Decline
(9) Undetermined Pattern
(8) Undetermined - not enough data

Maximum lung growth attained: (1) Yes (0) No
Plateau started: (2) No plateau (1) Yes (0) No
Decline started: (1) Yes (0) No

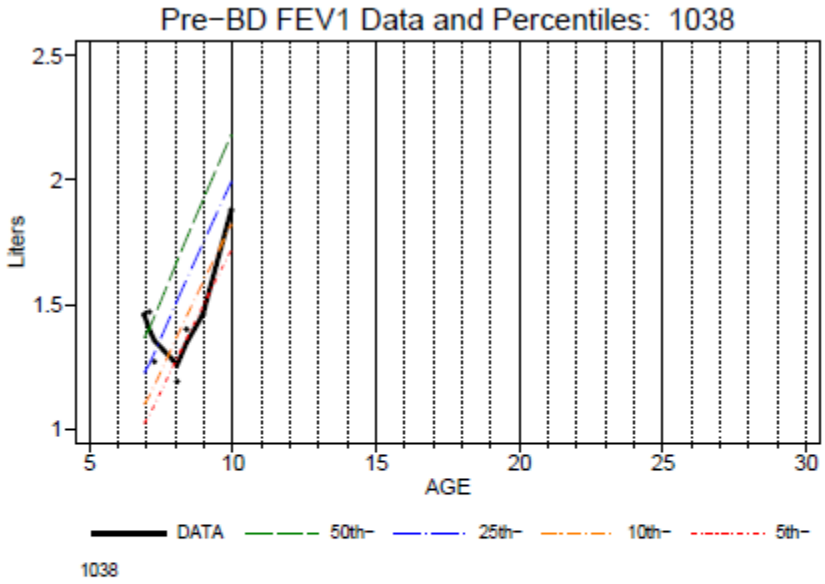
AGE AT each of the following periods (use '99' if N/A):

Maximum Lung Growth: ___ ___ . ___

Start of Plateau: ___ ___ . ___

Start of Decline: ___ ___ . ___

Example 3B: Sparse Data



PATTERN OF GROWTH/DECLINE (Check One)
(1) Normal Growth
(2) Normal Growth, Early Decline
(3) Reduced Growth
(4) Reduced Growth, Early Decline
(9) Undetermined Pattern
(8) Undetermined - not enough data

Maximum lung growth attained: (1) Yes (0) No
Plateau started: (2) No plateau (1) Yes (0) No
Decline started: (1) Yes (0) No

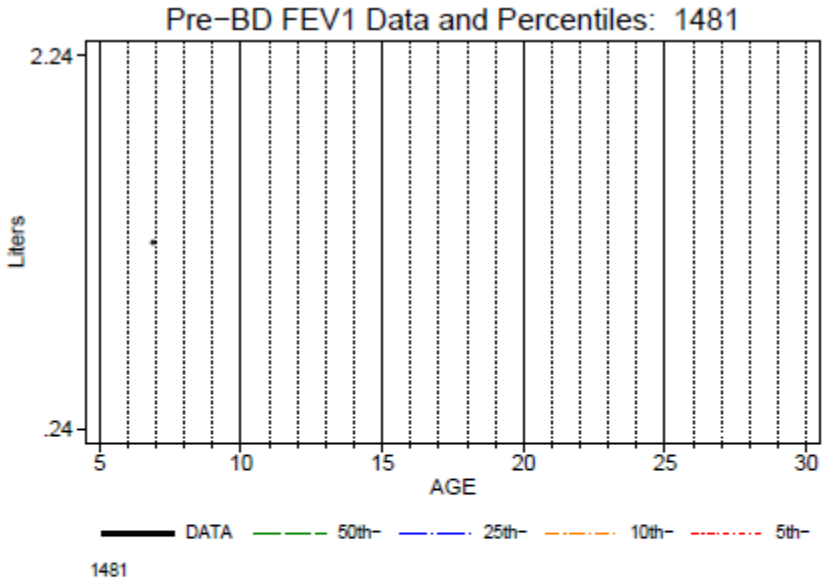
AGE AT each of the following periods (use '99' if N/A):

Maximum Lung Growth: ___ ___ . ___

Start of Plateau: ___ ___ . ___

Start of Decline: ___ ___ . ___

Example 3C: Sparse Data



PATTERN OF GROWTH/DECLINE (Check One)
(1) Normal Growth
(2) Normal Growth, Early Decline
(3) Reduced Growth
(4) Reduced Growth, Early Decline
(9) Undetermined Pattern
(8) Undetermined - not enough data

Maximum lung growth attained: (1) Yes (0) No
Plateau started: (2) No plateau (1) Yes (0) No
Decline started: (1) Yes (0) No

AGE AT each of the following periods (use '99' if N/A):

Maximum Lung Growth: ___ ___ . ___

Start of Plateau: ___ ___ . ___

Start of Decline: ___ ___ . ___

Example 4A: NG, no maximum lung function

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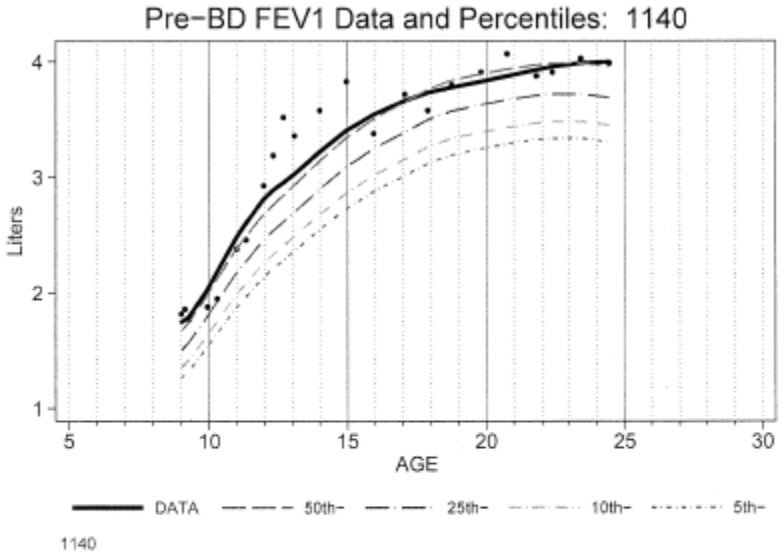

ATTERN OF GROWTH/DECLINE (Check One)
(1) Normal Growth
(2) Normal Growth, Early Decline
(3) Reduced Growth
(4) Reduced Growth, Early Decline
(9) Undetermined Pattern
(8) Undetermined - not enough data

Maximum lung growth attained: (1) Yes ( ) No
Plateau started: (2) No plateau (1) Yes ( ) No
Decline started: (1) Yes ( ) No

AGE AT each of the following periods (use '99' if N/A):

Maximum Lung Growth: 99.__
Start of Plateau: 99.__
Start of Decline: 99.__

Example 4B: NG, maximum lung function growth attained

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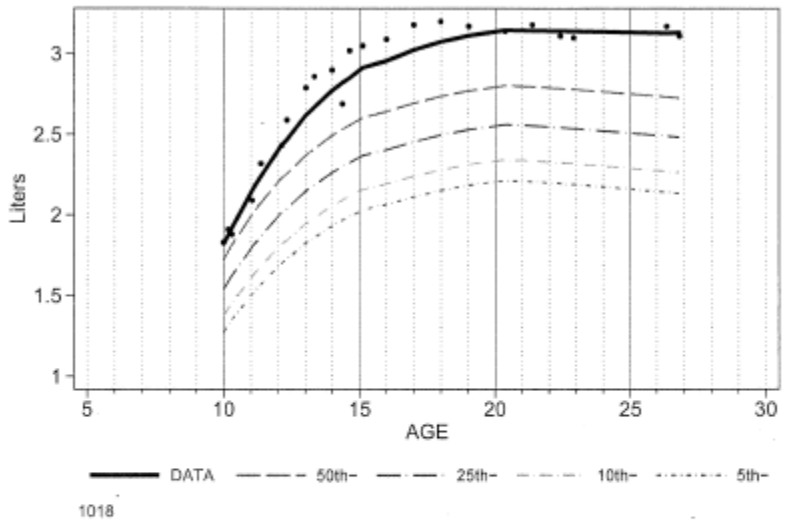
Pre−BD FEV1 Data and Percentiles: 1018



1018

PATTERN OF GROWTH/DECLINE (Check One)
- (✓1) Normal Growth
- (2) Normal Growth, Early Decline
- (3) Reduced Growth
- (4) Reduced Growth, Early Decline
- (9) Undetermined Pattern
- (8) Undetermined - not enough data

Maximum lung growth attained: (✓1) Yes (0) No
Plateau started: (2) No plateau (✓1) Yes (0) No
Decline started: (1) Yes (✓0) No

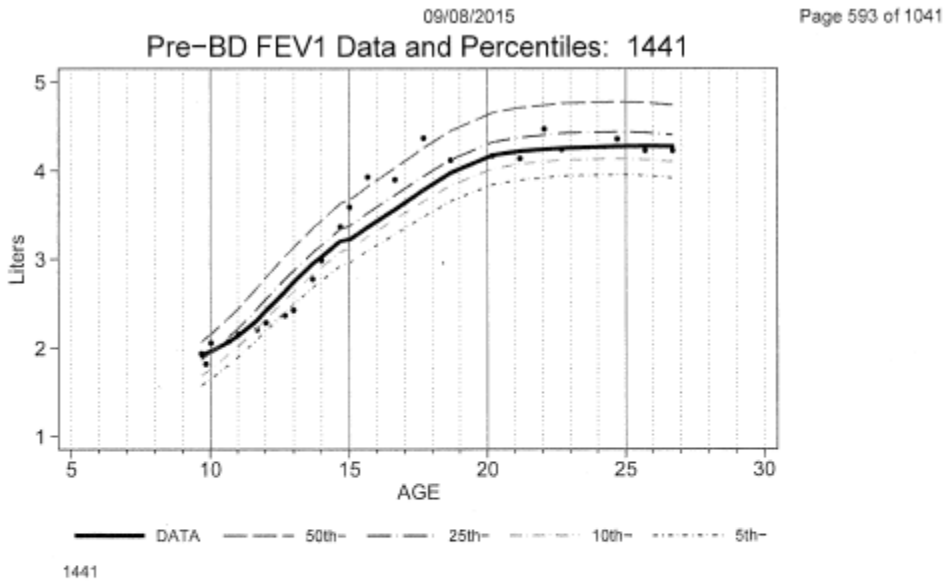
AGE AT each of the following periods (use '99' if N/A):

Maximum Lung Growth: 20.0

Start of Plateau: 20.0

Start of Decline: 99.

Example 4C: RG, plateau begun



PATTERN OF GROWTH/DECLINE (Check One)
- (1) Normal Growth
- (2) Normal Growth, Early Decline
- (✓3) Reduced Growth
- (4) Reduced Growth, Early Decline
- (9) Undetermined Pattern
- (8) Undetermined - not enough data

Maximum lung growth attained: (✓1) Yes (0) No
Plateau started: (2) No plateau (✓1) Yes (0) No
Decline started: (1) Yes (✓0) No

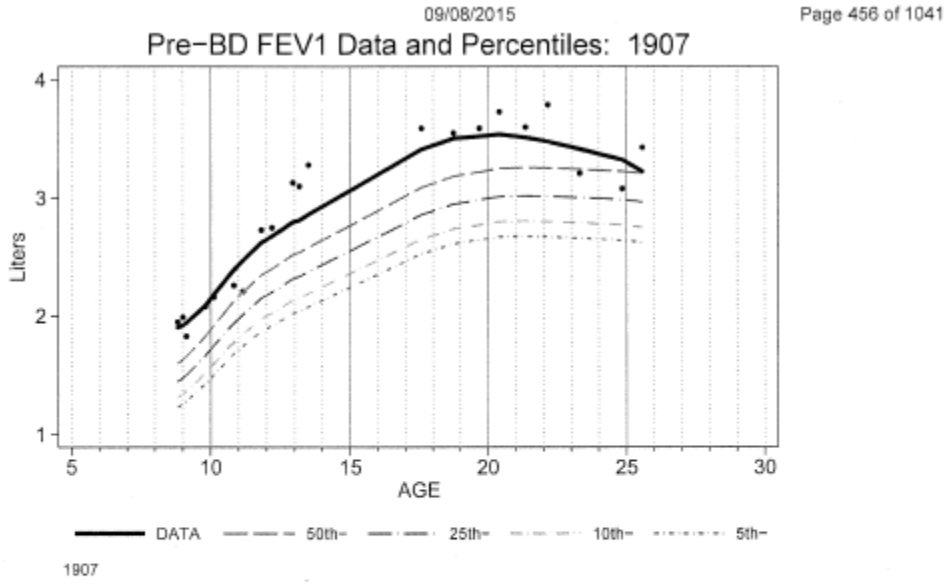
AGE AT each of the following periods (use '99' if N/A):

Maximum Lung Growth: 23.0

Start of Plateau: 23.0

Start of Decline: 99.

Example 4D: NG/ED, with an immediate decline



PATTERN OF GROWTH/DECLINE (Check One)
- (1) Normal Growth
- (✓2) Normal Growth, Early Decline
- (3) Reduced Growth
- (4) Reduced Growth, Early Decline
- (9) Undetermined Pattern
- (8) Undetermined - not enough data

Maximum lung growth attained: (✓1) Yes (0) No
Plateau started: (✓2) No plateau (1) Yes (0) No
Decline started: (✓1) Yes (0) No

AGE AT each of the following periods (use '99' if N/A):

Maximum Lung Growth: 20.3
Start of Plateau: 99.__
Start of Decline: 20.3

Example 4E: RG, maximum lung function not attained, no plateau or decline started

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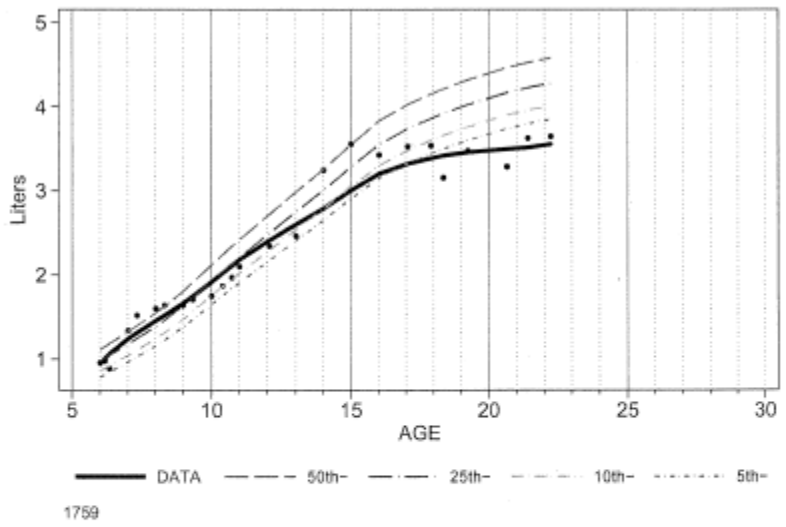

PATTERN OF GROWTH/DECLINE (Check One)
- (1) Normal Growth
- (2) Normal Growth, Early Decline
- (✓3) Reduced Growth
- (4) Reduced Growth, Early Decline
- (9) Undetermined Pattern
- (8) Undetermined - not enough data

Maximum lung growth attained: (1) Yes (✓0) No
Plateau started: (2) No plateau (1) Yes (✓0) No
Decline started: (1) Yes (✓8) No

AGE AT each of the following periods (use '99' if N/A):

Maximum Lung Growth: 99.__
Start of Plateau: 99.__
Start of Decline: 99.__

Supplementary Appendix 2. Pattern coding sheets for the 1041 CAMP participants. See Supplementary Data File *Appendix2B.CAMPcodingSheets.pdf*

Part 3. Public use data file of 1041 CAMP participants' pattern and spirometry data

Supplementary Appendix 3. CAMP patterns and spirometry public use data dictionary.

Supplementary Appendix 4. CAMP patterns and spirometry public use data file.

SAS Output file *CAMPPDFLinkage.xpt* contains the pattern code, age, spirometry measures and the NHANES III expected spirometry values at each spirometry visit of follow-up for the 1041 CAMP participants. Each participant is identified by a unique random ID which is the same ID used for the pattern coding sheets located in Supplementary Appendix 2, and the CAMP study public use data files located at the NHLBI BioLINCC Repository. The file *CAMPPDFLinkage.contents.pdf* contains the data dictionary and explanations of data contained in *CAMPPDFLinkage.xpt.*