CHEST Online Supplement

Asthma Is a Risk Factor for Respiratory Exacerbations Without Increased Rate of Lung Function Decline

Five-Year Follow-up in Adult Smokers From the COPDGene Study

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e-Appendix 1: Institutional Review Board Approval

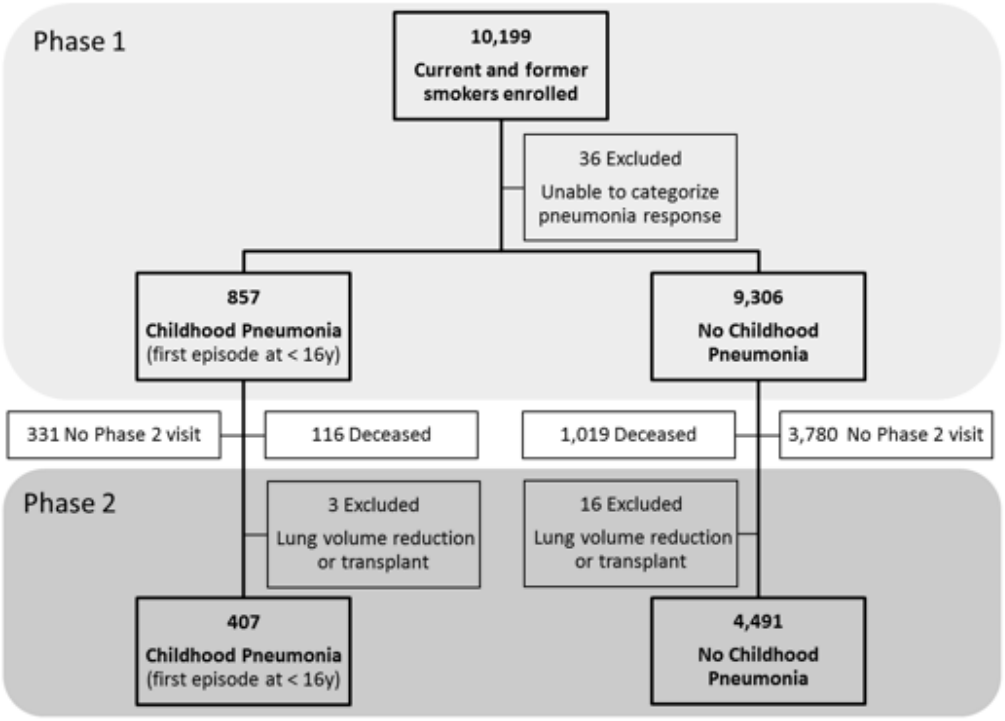
This study was conducted in accordance with the amended Declaration of Helsinki. This study obtained approval from the Institutional Review Board at Brigham and Women's Hospital and at each of the twenty-one clinical sites. All participants provided written informed consent for their medical data to be used prior to taking part in the study.

Clinical Center and IRB protocol numbers:

Ann Arbor VA, Ann Arbor, MI (PCC 2008-110732)
Baylor College of Medicine, Houston, TX (H-22209)
Brigham and Women's Hospital, Boston, MA (2007-P-000554/2; BWH)
Columbia University, New York, NY (IRB-AAAC9324)
Duke University Medical Center, Durham, NC (Pro00004464)
Health Partners Research Foundation, Minneapolis, MN (07-127)
Johns Hopkins University, Baltimore, MD (NA_00011524)
Los Angeles Biomedical Research Institute at Harbor UCLA Medical Center, Los Angeles, CA (12756-01)
Michael E. DeBakey VAMC, Houston, TX (H-22202)
Minneapolis VA, Minneapolis, MN (4128-A)
Morehouse School of Medicine, Atlanta, GA (07-1029)
National Jewish Health, Denver, CO (HS-1883a)
Reliant Medical Group, Worcester, MA (1143)
Temple University, Philadelphia, PA (11369)
University of Alabama, Birmingham, AL (FO70712014)
University of California, San Diego, CA (70876)
University of Iowa, Iowa City, IA (200710717)
University of Michigan, Ann Arbor, MI (HUM00014973)
University of Minnesota, Minneapolis, MN (0801M24949)
University of Pittsburgh, Pittsburgh, PA (PRO07120059)
University of Texas Health Science Center at San Antonio, San Antonio, TX (HSC20070644H)

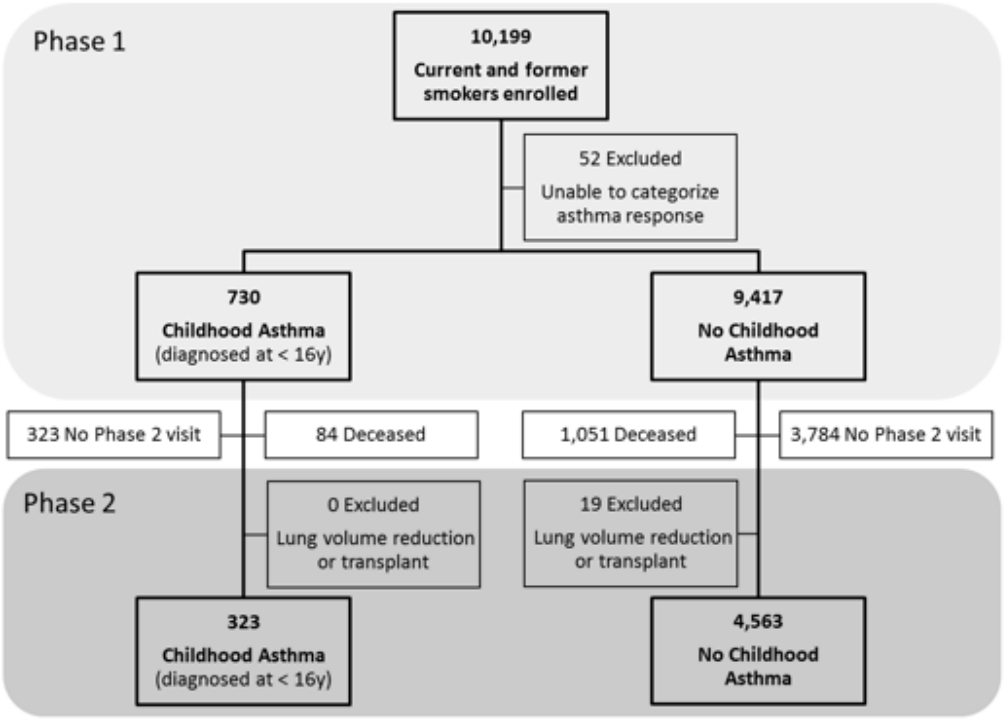
e-Figure 1: Flow Chart of Subjects Groupings For Each Analysis

Analysis (1)



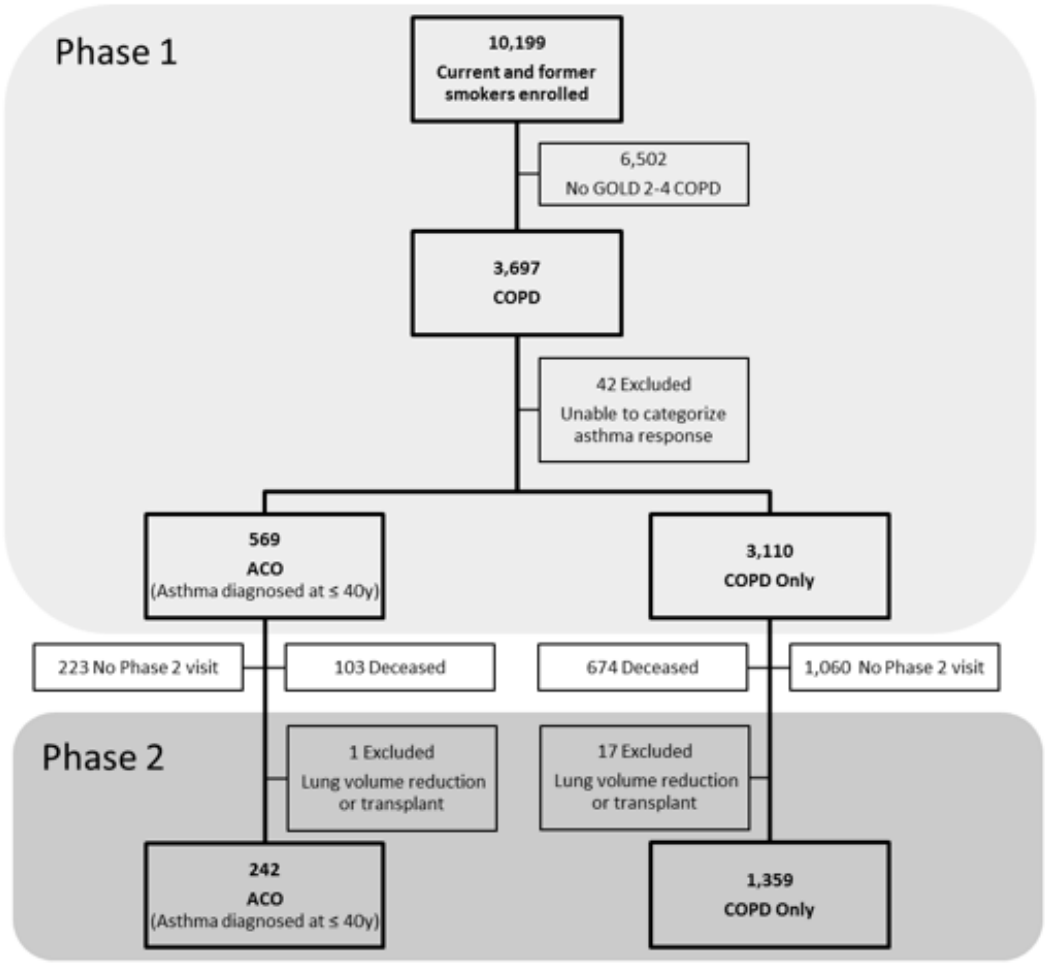
Childhood pneumonia analysis: Disease progression at Phase 2 in those with childhood pneumonia compared to those without childhood pneumonia.

Analysis (2)



Childhood asthma analysis: Disease progression at Phase 2 in those with childhood asthma compared to those without childhood asthma.

Analysis (3)



Asthma COPD Overlap (ACO) analysis: Disease progression at Phase 2 in those with ACO compared to those without COPD alone.

e-Table 1: Disease Progression in Childhood Pneumonia, Childhood Asthma and ACO, Univariate Analysis

	Childhood Pneumonia	No Childhood Pneumonia	P	Childhood Asthma	No Childhood Asthma	P	ACO	No ACO	P
Phase 1	N = 857	N = 9306		N = 730	N = 9417		N = 569	N = 3110	
Deceased as of September 2016 (%)[a]	116 (14%)	1019 (11%)	0.04	84 (12%)	1051 (11%)	0.44	103 (18%)	674 (22%)	0.19
Phase 2 (%)[a]	407 (47%)	4491 (48%)	0.69	323 (44%)	4563 (48%)	0.03	242 (43%)	1359 (44%)	0.64
Lung Function and Clinical Symptoms									
Developed COPD (%)[a]	30 (7%)	313 (7%)	0.84	27 (8%)	317 (7%)	0.40	NA	NA	
Developed oxygen requirement (%)[a]	32 (8%)	286 (6%)	0.28	23 (7%)	295 (6%)	0.71	33 (14%)	207 (15%)	0.61
Developed chronic bronchitis (%)[a]	31 (8%)	359 (8%)	0.99	28 (9%)	359 (8%)	0.42	24 (10%)	155 (11%)	0.78
Had a severe exacerbation in prior yr (%)[a]	48 (12%)	411 (9%)	0.10	52 (16%)	406 (9%)	<0.001	60 (25%)	237 (17%)	0.009
# of exacerbations in prior yr, mean (SD)[b]	0.42 (0.86)	0.30 (0.79)	<0.001	0.59 (1.08)	0.29 (0.77)	<0.001	0.81 (1.23)	0.56 (1.03)	<0.001
FEV_1 post-BD % predicted, mean Δ (SD)[c]	-1.64 (11)	-1.98 (11)	<0.001	-1.48 (12)	-1.98 (10)	<0.001	-2.53 (11)	-2.64 (11)	<0.001
FEV_1 post-BD mL, mean Δ (SD)[c]	-196 (279)	-202 (287)	<0.001	-168 (303)	-204 (284)	<0.001	-160 (313)	-188 (306)	<0.001
FEV_1 post-BD mL/year, mean Δ (SD)[c]	-36 (53)	-37 (53)	<0.001	-31 (54)	-38 (53)	<0.001	-30 (56)	-35 (57)	<0.001
FVC post-BD % predicted, mean Δ (SD)[c]	-1.83 (12)	-2.11 (12)	<0.001	-0.73 (13)	-2.15 (12)	<0.001	-2.81 (14)	-3.69 (14)	<0.001
FVC post-BD mL, mean Δ (SD)[c]	-250 (417)	-248 (424)	<0.001	-188 (432)	-252 (421)	<0.001	-239 (466)	-314 (506)	<0.001
FVC ml/year, mean Δ (SD)[c]	-47 (79)	-46 (80)	<0.001	-35 (81)	-47 (80)	<0.001	-44 (86)	-59 (96)	<0.001
SGRQ score, mean Δ (SD)[c]	-0.57 (17)	0.29 (15)	0.57	-2.22 (18)	0.39 (15)	0.52	-1.09 (17)	1.84 (15)	0.80
MMRC dyspnea scale, mean Δ (SD)[c]	-0.05 (1.13)	0.07 (1.24)	0.15	-0.02 (1.26)	0.07 (1.23)	0.61	0.09 (1.26)	0.22(1.29)	<0.001
Δ 6 minute walk (SD)[c]	-154 (333)	-129 (363)	<0.001	-151 (385)	-130 (360)	<0.001	-156 (356)	-189 (370)	<0.001
Chest CT Scan Measurements									
PRM Emphysema % at -950HU, mean Δ (SD)[c]	0.45 (4)	0.71 (3)	<0.001	0.61 (4)	0.68 (3)	<0.001	1.14 (5)	2.14 (5)	<0.001
Adjusted density, mean Δ (SD)[c]	-0.05 (12)	-0.83 (11)	<0.001	-1.33 (12)	-0.72 (11)	<0.001	-2.05 (11)	-3.32 (11)	<0.001
Gas Trapping %, Exp – 856HU, mean Δ (SD)[c]	1.14 (9)	1.21 (9)	<0.001	1.19 (9)	1.19 (9)	<0.001	1.57 (11)	3.72 (10)	<0.001
PRM functional SAD, mean Δ (SD)[c]	1.09 (7)	0.92 (7)	<0.001	0.97 (8)	0.93 (7)	<0.001	0.96 (9)	2.12 (8)	<0.001
SRWA-Pi10 (SD), mean Δ (SD)[c]	0.06 (0.29)	0.04 (0.30)	<0.001	0.07 (0.33)	0.04 (0.30)	0.01	0.08 (0.36)	0.03 (0.34)	<0.001

Abbreviations: *COPD* chronic obstructive pulmonary disease; *ACO* Asthma-COPD overlap; *P* p-value; *yr* year; *SD* standard deviation; *FEV_1* forced expiratory volume in the first second; *BD* bronchodilator; *FVC* forced vital capacity; *SGRQ* St. George's Respiratory Questionnaire; *MMRC* Modified Medical Research Council; *CT* computed tomography; *PRM* parametric response mapping; *HU* Hounsfield units; *Exp* Expiration; *SAD* small airways disease; *SRWA-Pi10* square root wall area of a hypothetical airway with 10mm internal perimeter. Univariate analysis with: [a] Chi-square, [b] Wilcoxon rank sum test, [c] t-test.

e-Table 2: Exacerbations in COPD Subjects with Childhood Pneumonia and Childhood Asthma

	Childhood Pneumonia	No Childhood Pneumonia	Impact of Childhood Pneumonia[a]			Childhood Asthma	No Childhood Asthma	Impact of Childhood Asthma[a]		
	N = 175	N = 1429				N = 152	N = 1446			
			OR	95% CI	P			OR	95% CI	P
Had a severe COPD exacerbation in prior yr (%)[b,e,f,g,h]	37 (21%)	258 (18%)	1.29	(0.85 - 1.92)	0.22	29 (19%)	265 (18%)	0.96	(0.61 - 1.48)	0.86
			β	SE	P			β	SE	P
Number of COPD exacerbations in prior yr, mean (SD)[c,e,f,g,h]	0.77 (1.06)	0.57 (1.07)	0.17	0.08	0.04	0.74 (1.19)	0.58 (1.05)	0.14	0.09	0.12
FEV_1 post-BD % predicted, mean Δ (SD)[d,e]	-2.24 (11)	-2.74 (11)	0.49	0.88	0.58	-1.81 (11)	-2.72 (11)	0.92	0.93	0.32
FEV_1 post-BD mL, mean Δ (SD)[d,e,f,i]	-180 (269)	-186 (313)	11.52	25.06	0.65	-147 (310)	-188 (307)	36.27	26.50	0.17
FVC post-BD % predicted, mean Δ (SD)[d,e]	-3.09 (13)	-3.72 (14)	0.61	1.12	0.59	-1.63 (14)	-3.77 (14)	2.14	1.18	0.07
FVC post-BD mL, mean Δ (SD)[d,e,f,i]	-296 (462)	-307 (507)	19.68	41.43	0.63	-213 (480)	-313 (502)	91.64	43.73	0.04

Abbreviations: *COPD* chronic obstructive pulmonary disease; *P* p-vlaue; *yr* year; *SD* standard deviation. [a] Each row is a separate model: [b] Logistic regression with odds ratio (OR), 95 % confidence interval (CI);[c] Linear regression with beta coefficient (β), standard error (SE) and [d] Linear mixed model with beta coefficient (β), standard error (SE). Adjusted for: [e] pack years of smoking; [f] gender, age, race; [g] FEV_1 % predicted; [h] current smoking; [i] height.