Online Supplemental Data

Early-Onset COPD is Associated with Female Gender, Maternal Factors, and African American Race in the COPDGene Study

Marilyn G. Foreman, Lening Zhang, James Murphy, Nadia N. Hansel, Barry Make, John E. Hokanson, George Washko, Elizabeth A. Regan, James D. Crapo, Edwin K. Silverman, Dawn L. DeMeo and the COPDGene Investigators

Severe Early-Onset COPD Defined as FEV_1 Percent Predicted < 40% and Age < 53 Years

More closely adherent to the original enrollment criteria for the Boston Early-Onset COPD Study,[5] 34 (1.4%) of the initial 2500 subjects enrolled into the COPDGene Study presented with an FEV_1 percent predicted < 40% and age < 53 years. Of these subjects, 22/34 (65%) were female and 11/34 (32%) were African American. In comparison to older COPD subjects who also exhibited an FEV_1 percent predicted < 40%, these individuals initiated smoking at a younger age, 15 $\pm$ 3 vs. 17 $\pm$ 4 years ($p = 0.004$) and smoked less, 38 vs. 64 (mean) pack-years ($p < 0.0001$), but were more likely to be current smokers, 50 vs. 13%, $p < 0.0001$. They were significantly younger at age at first pneumonia, 34 vs. 46 (mean) years ($p = 0.009$). The MMRC dyspnea score ($p = 0.4$) and the six-minute walk distance ($p = 0.7$) were not significantly different. CT percent gas trapping ($p = 0.06$) did not differ but CT percent emphysema was lower, 21 vs. 27% ($p = 0.03$).

A history of asthma was not significantly different ($p = 0.06$). Maternal smoking, 74% vs. 44% ($p = 0.001$) and maternal asthma, 19 vs. 4% ($p = 0.009$) were proportionally more frequent. There were no significant associations with paternal factors in these severe COPD subjects.

Table E1. Severe COPD Subjects
COPDGene Study
Age < 53 Years and FEV_1 < 40% Predicted

	Early-Onset (n = 34)	Older COPD Subjects > 64 years (n = 205)	p-value
Age (years)	49 ± 3	70 ± 4	<0.0001
Gender (% female)	65	41	0.001
Pack-years of smoking (mean ± sd)	38 ± 22	64 ± 29	<0.0001
Maternal COPD (%)	23	12	0.1
Maternal smoking (%)	74	44	0.001
Maternal lung cancer	11	6	0.4
Paternal COPD (%)	21	13	0.3
Paternal smoking (%)	83	80	0.8
MMRC dyspnea score	3.1 ± 0.9	2.9 ± 1.0	0.4
FEV_1 percent predicted	27 ± 8	29 ± 7	0.4
BMI	26 ± 7	26 ± 5	0.9
BODE Index	5.4 ± 1.2	5.1 ± 1.4	0.3
CT scan percent emphysema	21 ± 14	27 ± 13	0.03
CT scan percent gas trapping	54 ± 19	61 ± 14	0.06

Table E2. Selected questions from the COPDGene Respiratory Questionnaire

1. Do you usually have a cough? (Exclude clearing of throat.)
2. For how many years have you had this cough?
3. Do you usually bring up phlegm from your chest?
4. For how many years have you had trouble with phlegm?
5. Have you ever had asthma?
6. Have you ever had pneumonia or bronchopneumonia?
7. Did your mother smoke cigarettes when she was pregnant with you?
8. Were either of your natural parents told by a doctor they had a chronic lung condition such as:
   Chronic bronchitis
   Emphysema
   COPD
   Asthma
   Lung cancer
9. Were either of your natural parents ever a cigarette smoker?

Table E3. Additional Logistic Regression Models for Severe Early-Onset COPD in the COPDGene Study

Model E3.A				
Univariate Analyses			Multivariable Models	
Characteristic	OR (95% CI)	p-value	OR (95% CI)	p-value
Female gender (47)	2.6 (1.5 – 4.5)	0.0006	3.9 (1.4 – 10.8)	0.009
AA race (16)	4.4 (2.4 – 8.1)	<0.0001	8.0 (2.5 – 25.5)	0.0005
Smoking intensity	0.6 (0.3 – 1.0)	0.04	0.8 (0.3 – 1.9)	0.5
Maternal COPD (14)	2.2 (1.1 – 4.5)	0.03	3.5 (0.98 – 12.4)	0.055
Maternal smoking (49)	2.9 (1.7 – 5.1)	0.0002	1.8 (0.6 – 4.9)	0.3
Multivariable model E3.A: race, gender, daily smoking intensity, maternal COPD, maternal smoking, and clinical center (Hosmer-Lemeshow p = 0.9)				
Model E3.B				
Univariate Analyses			Multivariable Models	
Female gender (47)	2.6 (1.5 – 4.5)	0.0006	3.6 (1.3 – 10)	0.02
AA race (16)	4.4 (2.4 – 8.1)	<0.0001	7.4 (2.2 – 25)	0.001
Maternal COPD composite (19)	2.1 (1.1 – 4.1)	0.02	6.4 (1.8 – 22)	0.004
Maternal Smoking (49)	2.9 (1.7 – 5.1)	0.002	1.4 (0.5 – 4.0)	0.6
Pack-years of smoking	0.97 (0.96 – 0.98)	<0.0001	0.98 (0.95 – 1.0)	0.03
Advanced education (56)	0.4 (0.3 – 0.7)	0.002	0.7 (0.3 – 1.7)	0.4
Multivariable model E3.B: race, gender, maternal OLD, advanced education, and clinical center (Hosmer-Lemeshow p = 0.1)				

Clinical center, not displayed, was not significant in either multivariable model.

AA = African American
COPD composite = variable composed of reports of maternal COPD, chronic bronchitis, emphysema
Smoking intensity = $\geq$ 20 cigarettes daily vs. less

Table E4. Predictors of Severe COPD (FEV_1 percent predicted < 50) by Age Groups in the COPDGene Study

Characteristic (%)	Univariate Analyses (n = 2500)		Age < 55 Years		Age 55 – 64 Years		Age > 64 Years	
	OR (CI)	p-value	OR (CI)	p-value	OR (CI)	p-value	OR (CI)	p-value
Maternal COPD (16)	2.1 (1.5 – 2.8)	<0.0001	3.2 (1.2 – 8.7)	0.02	2.2 (1.1 – 4.6)	0.04	2.9 (1.3 – 6.5)	0.001
Gender (47)	1.1 (0.9 – 1.3)	0.3	3.1 (1.3 – 7.7)	0.02	0.96 (0.6 – 1.6)	0.9	0.7 (0.50 – 0.98)	0.04
Pack-years	1.02 (1.015 – 1.022)	<0.0001	1.04 (1.01 – 1.06)	0.001	1.01 (1.0 – 1.02)	0.01	1.01 (1.0 – 1.02)	0.0005
Race [≠] (16)	1.9 (1.5 – 2.4)	<0.0001	0.7 (0.3 – 1.8)	0.5	1.2 (0.7 – 2.1)	0.6	0.9 (0.5 – 1.8)	0.8
Hosmer-Lemeshow goodness-of-fit test			p = 0.8		p = 0.5		p = 0.04	

For each age group, the models included the covariates used in the analyses for early-onset COPD: race, gender, maternal COPD, maternal smoking, and pack-years of smoking, utilizing a stepwise selection algorithm with a p = 0.1 threshold for retention. Because clinical center and maternal smoking were not selected in the stepwise algorithms, they are not displayed here. The reference groups of control smokers were in the same age range as the early-onset subjects in each tertile.

[≠]Odds ratios displayed for African American race
[§]Baylor College of Medicine was the reference clinical center

Table E5. Clinical Investigators / Clinical Centers

The members of the COPDGene study group as of June 2010

Ann Arbor VA: Jeffrey Curtis, MD (PI), Ella Kazerooni, MD (RAD)

Baylor College of Medicine, Houston, TX: Nicola Hanania, MD, MS (PI), Philip Alapat, MD, Venkata Bandi, MD, Kalpalatha Guntupalli, MD, Elizabeth Guy, MD, Antara Mallampalli, MD, Charles Trinh, MD (RAD), Mustafa Atik, MD

Brigham and Women's Hospital, Boston, MA: Dawn DeMeo, MD, MPH (Co-PI), Craig Hersh, MD, MPH (Co-PI), George Washko, MD, Francine Jacobson, MD, MPH (RAD)

Columbia University, New York, NY: R. Graham Barr, MD, DrPH (PI), Byron Thomashow, MD, John Austin, MD (RAD)

Duke University Medical Center, Durham, NC: Neil MacIntyre, Jr., MD (PI), Lacey Washington, MD (RAD), H Page McAdams, MD (RAD)

Fallon Clinic, Worcester, MA: Richard Rosiello, MD (PI), Timothy Bresnahan, MD (RAD)

Health Partners Research Foundation, Minneapolis, MN: Charlene McEvoy, MD, MPH (PI), Joseph Tashjian, MD (RAD)

Johns Hopkins University, Baltimore, MD: Robert Wise, MD (PI), Nadia Hansel, MD, MPH, Robert Brown, MD (RAD), Gregory Diette, MD

Los Angeles Biomedical Research Institute at Harbor UCLA Medical Center, Los Angeles, CA: Richard Casaburi, MD (PI), Janos Porszasz, MD, PhD, Hans Fischer, MD, PhD (RAD), Matt Budoff, MD

Michael E. DeBakey VAMC, Houston, TX: Amir Sharafkhaneh, MD (PI), Charles Trinh, MD (RAD), Hirani Kamal, MD, Roham Darvishi, MD

Minneapolis VA: Dennis Niewoehner, MD (PI), Tadashi Allen, MD (RAD), Quentin Anderson, MD (RAD), Kathryn Rice, MD

Morehouse School of Medicine, Atlanta, GA: Marilyn Foreman, MD, MS (PI), Gloria Westney, MD, MS, Eugene Berkowitz, MD, PhD (RAD)

National Jewish Health, Denver, CO: Russell Bowler, MD, PhD (PI), Adam Friedlander, MD, David Lynch, MB (RAD), Joyce Schroeder, MD (RAD), John Newell, Jr., MD (RAD)

Temple University, Philadelphia, PA: Gerard Criner, MD (PI), Victor Kim, MD, Nathaniel Marchetti, DO, Aditi Satti, MD, A. James Mamary, MD, Robert Steiner, MD (RAD), Chandra Dass, MD (RAD)

University of Alabama, Birmingham, AL: William Bailey, MD (PI), Mark Dransfield, MD (Co-PI), Hrudaya Nath, MD (RAD)

University of California, San Diego, CA: Joe Ramsdell, MD (PI), Paul Friedman, MD (RAD)

University of Iowa, Iowa City, IA: Geoffrey McLennan, MD, PhD (PI), Edwin JR van Beek, MD, PhD (RAD), Brad Thompson, MD (RAD), Dwight Look, MD

University of Michigan, Ann Arbor, MI: Fernando Martinez, MD (PI), MeiLan Han, MD, Ella Kazerooni, MD (RAD)

University of Minnesota, Minneapolis, MN: Christine Wendt, MD (PI), Tadashi Allen, MD (RAD)

University of Pittsburgh, Pittsburgh, PA: Frank Sciurba, MD (PI), Joel Weissfeld, MD, MPH, Carl Fuhrman, MD (RAD), Jessica Bon, MD

University of Texas Health Science Center at San Antonio, San Antonio, TX: Antonio Anzueto, MD (PI), Sandra Adams, MD, Carlos Orozco, MD, Mario Ruiz, MD (RAD)

Administrative Core: James Crapo, MD (PI), Edwin Silverman, MD, PhD (PI), Barry Make, MD, Elizabeth Regan, MD, Sarah Moyle, MS, Douglas Stinson

Genetic Analysis Core: Terri Beaty, PhD, Barbara Klanderman, PhD, Nan Laird, PhD, Christoph Lange, PhD, Michael Cho, MD, Stephanie Santorico, PhD, John Hokanson, MPH, PhD, Dawn DeMeo, MD, MPH, Nadia Hansel, MD, MPH, Craig Hersh, MD, MPH, Jacqueline Hetmanski, MS, Tanda Murray

Imaging Core: David Lynch, MB, Joyce Schroeder, MD, John Newell, Jr., MD, John Reilly, MD, Harvey Coxson, PhD, Philip Judy, PhD, Eric Hoffman, PhD, George Washko, MD, Raul San Jose Estepar, PhD, James Ross, MSc, Rebecca Leek, Jordan Zach, Alex Kluiber, Jered Sieren, Heather Baumhauer, Verity McArthur, Dzimitry Kazlouski, Andrew Allen, Tanya Mann, Anastasia Rodionova

PFT QA Core, LDS Hospital, Salt Lake City, UT: Robert Jensen, PhD

Biological Repository, *Johns Hopkins University, Baltimore, MD*: Homayoon Farzadegan, PhD, Stacey Meyerer, Shivam Chandan, Samantha Bragan

Data Coordinating Center and Biostatistics, *National Jewish Health, Denver, CO*: James Murphy, PhD, Douglas Everett, PhD, Carla Wilson, MS, Ruthie Knowles, Amber Powell, Joe Piccoli, Maura Robinson, Margaret Forbes, Martina Wamboldt

Epidemiology Core, *University of Colorado School of Public Health, Denver, CO*: John Hokanson, MPH, PhD, Marci Sontag, PhD, Jennifer Black-Shinn, MPH, Gregory Kinney, MPH