3. Jakkula M, Le Cras TD, Gebb S, Hirth KP, Tuder RM, Voelkel NF, *et al*. Inhibition of angiogenesis decreases alveolarization in the developing rat lung. *Am J Physiol Lung Cell Mol Physiol* 2000;279:L600–L607.
4. Kasahara Y, Tuder RM, Taraseviciene-Stewart L, Le Cras TD, Abman S, Hirth PK, *et al*. Inhibition of VEGF receptors causes lung cell apoptosis and emphysema. *J Clin Invest* 2000;106:1311–1319.
5. Bilan VP, Schneider F, Novelli EM, Kelley EE, Shiva S, Gladwin MT, *et al*. Experimental intravascular hemolysis induces hemodynamic and pathological pulmonary hypertension: association with accelerated purine metabolism. *Pulm Circ* 2018;8:2045894018791557.
6. Tuder RM, Zhen L, Cho CY, Taraseviciene-Stewart L, Kasahara Y, Salvemini D, *et al*. Oxidative stress and apoptosis interact and cause emphysema due to vascular endothelial growth factor receptor blockade. *Am J Respir Cell Mol Biol* 2003;29:88–97.
7. Taraseviciene-Stewart L, Kasahara Y, Alger L, Hirth P, Mc Mahon G, Waltenberger J, *et al*. Inhibition of the VEGF receptor 2 combined with chronic hypoxia causes cell death-dependent pulmonary endothelial cell proliferation and severe pulmonary hypertension. *FASEB J* 2001; 15:427–438.
8. Abe K, Toba M, Alzoubi A, Ito M, Fagan KA, Cool CD, *et al*. Formation of plexiform lesions in experimental severe pulmonary arterial hypertension. *Circulation* 2010;121:2747–2754.
9. Bonnet S, Provencher S, Guignabert C, Perros F, Boucherat O, Schermuly RT, *et al*. Translating research into improved patient care in pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2017;195:583–595.

Hypersensitivity Pneumonitis Mortality by Industry and Occupation

To the Editor:

We read with interest the research letter by Fernández Pérez and colleagues (1) and agree that population-level mortality from hypersensitivity pneumonitis (HP) has not been well characterized in the United States. However, the role of occupation in the development and severity of HP is well established (2–4). Occupational exposures are responsible for a substantial portion of HP cases, and it is important to monitor trends in morbidity and mortality so that prevention activities can be prioritized. To that end, we conducted a similar analysis of HP mortality data from 2003 to 2017 (ICD-10 code J67.x) while also taking available employment history into account.

We identified a similar demographic risk profile: 58% of decedents were male, 93% were white, and a high proportion lived in the Midwest or Northeast. Using data obtained from 21 states during 2003, 2004, and 2007–2013, we calculated proportionate mortality ratios (PMRs) by usual industry and occupation while adjusting for age, sex, and race. Among industries, the PMR was highest for animal production (PMR, 9.9; 95% confidence interval [CI], 5.1–17.3) and crop production (PMR, 5.2; 95% CI, 2.9–8.7), and among occupations, it was highest among farmers and ranchers (PMR, 7.9; 95% CI, 5.0–11.8).

Fernández Pérez and colleagues acknowledge that exposure information was not available in these data; however, because HP is often caused by workplace exposures, a decedent's work history is a significant factor that should be considered. The authors suggest that genetic differences among racial groups could play a role in determining susceptibility to HP. We think it is unlikely that the racial differences observed are the result of genetic factors. It is far more likely that this observation is confounded by associations with geographical clustering of agricultural industries and occupations that are associated with race, which are in turn associated with exposure to antigens primarily found in organic substances.

We applaud the authors for highlighting the public health importance of HP, especially because mortality has been increasing and the root cause of this increase is unknown. Collecting a thorough clinical and occupational history is key to diagnosing HP and identifying an inciting antigen. If an occupational cause is identified, the individual worker might benefit from exposure reduction or avoidance, and a workplace evaluation could be conducted to identify additional cases and assess exposure controls. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Noemi B. Hall, Ph.D.*
John M. Wood, M.S.
A. Scott Laney, Ph.D.
David J. Blackley, Dr.P.H.
National Institute for Occupational Safety and Health
Morgantown, West Virginia

ORCID ID: 0000-0002-6710-2015 (N.B.H.).

*Corresponding author (e-mail: nhall@cdc.gov).

References

1. Fernández Pérez ER, Sprunger D, Ratanawatkul P, Maier LA, Huie TJ, Swigris JJ, *et al*. Increasing hypersensitivity pneumonitis–related mortality in the United States from 1988 to 2016 [letter]. *Am J Respir Crit Care Med* 2019;199:1284–1287.
2. Bang KM, Weissman DN, Pinheiro GA, Antao VC, Wood JM, Syamlal G. Twenty-three years of hypersensitivity pneumonitis mortality surveillance in the United States. *Am J Ind Med* 2006;49:997–1004.
3. Quirce S, Vandenplas O, Campo P, Cruz MJ, de Blay F, Koschel D, *et al*. Occupational hypersensitivity pneumonitis: an EAACI position paper. *Allergy* 2016;71:765–779.
4. Feary JR, Szram J. Occupational hypersensitivity pneumonitis: what is the evidence, when to think of it, and what to do. *Clin Pulm Med* 2016;23: 23–29.

Reply to Hall *et al.*

From the Authors:

We welcome the comments by Dr. Hall and colleagues on our identified long-term trends in hypersensitivity pneumonitis (HP)

Originally Published in Press as DOI: 10.1164/rccm.201904-0810LE on May 3, 2019

This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0 (http://creativecommons.org/licenses/by-nc-nd/4.0/). For commercial usage and reprints, please contact Diane Gern (dgern@thoracic.org).

Originally Published in Press as DOI: 10.1164/rccm.201904-0876LE on May 3, 2019

mortality in the United States (1) and share the goal of improving our understanding of the burden of HP and increasing our awareness of this disease to improve diagnosis and treatment.

HP is assuredly a complex, multifaceted lung disease, involving both genetic and environmental risk factors. We agree that the racial differences observed in our study are not solely due to genetic factors. As noted in our Discussion, the contribution of specific exposures is an important but unmeasured variable in our study, and region-specific variations in HP mortality are almost certainly affected by differences in occupational exposure across states. However, regardless of ethnicity/race confounding bias by workplace exposure, genetic variation (which can be related to and differ by race) is likely one of the many risk factors that act together to cause disease and should be considered when interpreting epidemiological data. For example, significant ethnic/racial differences have been described in idiopathic pulmonary fibrosis that may be related to genetic differences (2), and differences in specific gene polymorphisms associated with susceptibility to HP have been observed both between groups with different ethnic backgrounds and within ethnic/racial groups (3–5). Further work is needed to fully understand the role of genetic variation in the molecular and cellular processes, clinical characteristics, and outcomes of HP.

We certainly agree that occupational exposures are an important contributor to the overall burden of HP in the United States and that they should always be considered in both individual and population studies. Since the 1980s, various agricultural activities, including crop and animal farming, have been the most frequently recorded industries and occupations on death certificates for individuals with HP. However, when studying the role of occupation, an important limitation of the National Occupational Mortality Surveillance database is that less than half of the states provide data on the usual industry and occupation of decedents (limiting generalizability). Importantly, in contrast to work-related HP, nonoccupational HP cases are not reportable and therefore are likely undercounted and underrepresented in assessments of the relative contribution of occupational and nonoccupational exposures responsible for HP cases nationwide (6).

We hope that the insight gained from our study and the complementary data of Hall and colleagues will serve as a call to state health department officials and federal agencies to revise key policies regarding disease surveillance programs, risk management, and enforcement of exposure limits, particularly in the agricultural sectors, in an effort to reduce the impact of HP in the country. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Evans R. Fernández Pérez, M.D., M.S.*
National Jewish Health
Denver, Colorado

David Sprunger, M.D.
University of Colorado at Boulder
Boulder, Colorado

Pailin Ratanawatkul, M.D.
Khon Kaen University Faculty of Medicine
Khon Kaen, Thailand

Lisa A. Maier, M.D., M.S.P.H.
University of Colorado at Boulder
Boulder, Colorado

Tristan J. Huie, M.D.
Jeffrey J. Swigris, D.O., M.S.
Joshua J. Solomon, M.D.
National Jewish Health
Denver, Colorado

Michael Mohning, M.D.
National Jewish Health
Denver, Colorado
and
University of Colorado at Boulder
Boulder, Colorado

Rebecca C. Keith, M.D.
Kevin K. Brown, M.D.
National Jewish Health
Denver, Colorado

ORCID ID: 0000-0001-7535-1591 (E.R.F.P.).

*Corresponding author (e-mail: fernandezevans@njhealth.org).

References

1. Fernández Pérez ER, Sprunger D, Ratanawatkul P, Maier LA, Huie TJ, Swigris JJ, *et al*. Increasing hypersensitivity pneumonitis–related mortality in the United States from 1988 to 2016 [letter]. *Am J Respir Crit Care Med* 2019;199:1284–1287.
2. Swigris JJ, Olson AL, Huie TJ, Fernandez-Perez ER, Solomon J, Sprunger D, *et al*. Ethnic and racial differences in the presence of idiopathic pulmonary fibrosis at death. *Respir Med* 2012;106:588–593.
3. Zúñiga J, Torres-García D, Jimenez L, Ramírez-Martínez G, Juárez-Nicolás F, Mujica F, *et al*. PDCD1 gene polymorphisms in different Mexican ethnic groups and their role in the susceptibility to hypersensitivity pneumonitis. *Clin Biochem* 2010;43:929–931.
4. Camarena A, Aquino-Galvez A, Falfán-Valencia R, Sánchez G, Montaño M, Ramos C, *et al*. PSMB8 (LMP7) but not PSMB9 (LMP2) gene polymorphisms are associated to pigeon breeder's hypersensitivity pneumonitis. *Respir Med* 2010;104:889–894.
5. Selman M, Pardo A, King TE Jr. Hypersensitivity pneumonitis: insights in diagnosis and pathobiology. *Am J Respir Crit Care Med* 2012;186: 314–324.
6. Fernández Pérez ER, Kong AM, Raimundo K, Koelsch TL, Kulkarni R, Cole AL. Epidemiology of hypersensitivity pneumonitis among an insured population in the United States: a claims-based cohort analysis. *Ann Am Thorac Soc* 2018;15:460–469.

Are Rural Residence and Poverty Independent Risk Factors for Chronic Obstructive Pulmonary Disease in the United States?

To the Editor:

With great interest, I read the article by Raju and colleagues (1) in which they concluded that living in a rural community and poverty were significantly associated with the incidence of chronic

Supported by the National Natural Science Foundation of China (81672820).

Originally Published in Press as DOI: 10.1164/rccm.201904-0829LE on May 20, 2019