5 consecutive years. Moreover, the age of the study subjects does not influence the serum sRAGE levels. Indeed, our data show no differences in serum sRAGE levels between young (average 23.5 yr) and old (average 54.7 yr) subjects in either the never-smokers group or the smokers group (Figure 1B). In addition, our young subjects were even younger than the study population of Biswas, which had an average age of 34.1 years. Our data therefore indicate that neither age nor chronic smoke exposure affects serum sRAGE levels. The discrepancy in study results when comparing the serum sRAGE levels in smokers and nonsmokers may be explained by our finding that smoking before blood sampling acutely decreases serum sRAGE levels (1). Therefore, controlling or monitoring smoking behavior before blood sampling may be used as a precautionary measure to decrease the variability between measurements and increase the value of sRAGE as a biomarker for COPD. Lastly, we agree with Biswas that more research is needed regarding the effect of smoking on serum sRAGE levels and the underlying mechanisms before sRAGE can be clinically used as a biomarker for COPD.

She corresponding author (e-mail: s.d.pouwels@umcg.nl).

ORCID ID: 0000-0001-7345-8061 (S.D.P.).

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

Simon D. Pouwels, Ph.D.*‡
Frank Klont, Ph.D.†
Marcel Kwiatkowski, Ph.D.
Valerie R. Wiersma, Ph.D.
University of Groningen
Groningen, the Netherlands

Corresponding author (e-mail: s.d.pouwels@umcg.nl).

References

1. Pouwels SD, Klont F, Kwiatkowski M, Wiersma VR, Faiz A, van den Berge M, et al. Cigarette smoking acutely decreases serum levels of the chronic obstructive pulmonary disease biomarker sRAGE. Am J Respir Crit Care Med 2018;198:1456–1458.

2. Prasad K, Dhar I, Caspar-Bell G. Role of advanced glycation end products and its receptors in the pathogenesis of cigarette smoke-induced cardiovascular disease. Int J Angiol 2015;24:75–80.

3. Biswas SK, Mudi SR, Mollah FH, Bierhaus A, Arslam MI. Serum soluble receptor for advanced glycation end products (sRAGE) is independently associated with cigarette smoking in non-diabetic healthy subjects. Diab Vasc Dis Res 2013;10:380–382.

4. Biswas SK. What does cigarette smoking do to the circulating level of soluble receptor for advanced glycation end products? Int J Angiol 2016;25:137–138.

5. Imkamp K, Berg M, Vermeulen CJ, Heijink IH, Guryev V, Kerstjens HAM, et al. Nasal epithelium as a proxy for bronchial epithelium for smoking-induced gene expression and expression Quantitative Trait Loci. J Allergy Clin Immunol 2018;142:314–317.e15, e15.

6. Klont F, Pouwels SD, Hermans J, van de Merbel NC, Horvatovich P, Ten Hacken NH, et al. A fully validated liquid chromatography-mass spectrometry method for the quantification of the soluble receptor of advanced glycation end-products (sRAGE) in serum using immunopurification in a 96-well plate format. Talanta 2018;182:414–421.

Copyright © 2019 by the American Thoracic Society

Socioeconomic Disparities and Health Outcomes

To the Editor:

The ability to link data from sources such as the U.S. Census is now enabling researchers to direct their focus toward reporting neighborhood and contextual characteristics that increase the risk for adverse health outcomes and are independent of patient-level attributes. This is all the more important because disparities in health outcomes likely arise as a result of both individual exposures and contextual factors (1). Research regarding disparities have until recently been challenging because of the high response bias associated with collecting individual-level socioeconomic measures (2). However, area-based measures from the U.S. Census’s American Community Survey and the National Center for Health Statistics Urban-Rural Classification Scheme can be used to gain insight into the role of area-based measures as independent risk factors for diseases, as demonstrated in the work by Raju and colleagues (3). Understanding area-based risk factors could help researchers design, target, monitor, and assess public health programs, including prevention interventions.

First, some limitations of Raju and colleagues’ analysis need to be emphasized. Although the authors used census tract-based determinants as area-based measures, it is important to acknowledge the possibility of ecological fallacy, and that these determinants provide information regarding the neighborhood that is not reducible to the individual level (4). Although the authors have defined neighborhoods as census tracts, nearby neighborhoods may also influence health outcomes and disparities.

Second, data structures arising from both individual and neighborhood levels are inherently hierarchical and correlated. To account for geographical correlation, it is important to analyze such data using multilevel models. Multilevel models can account for the lack of independence, evaluate multivariate associations, incorporate covariates at both individual and geographic levels, and model interactions between variables (5). Multilevel models have been used to evaluate health disparities and to describe the relationship between geographic exposures for a wide variety of health outcomes. They can also help researchers quantify the proportion of variability associated with being in a specific neighborhood.

The authors are to be applauded for taking the research on chronic obstructive pulmonary disease risk factors a step further by investigating...
area-based measures. Although the availability of public datasets such as those provided by the U.S. Census make such investigations possible, it must be emphasized that their implementation is challenging. Several resources, such as the Public Health Disparities Geocoding Project (6), are available to provide guidance on techniques to conduct research on socioeconomic gradients in health.

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

Rameela Chandrasekhar, Ph.D.*
Vanderbilt University School of Medicine
Nashville, Tennessee

ORCID ID: 0000-0002-1230-1068 (R.C.).

*Corresponding author (e-mail: rameela.chandrasekhar@vanderbilt.edu).

References

1. Morenoff JD, Lynch JW. What makes a place healthy? Neighborhood influences on racial/ethnic disparities in health over the life course. In: National Research Council (US) Panel on Race, Ethnicity, and Health in Later Life; Anderson NB, Bulatao RA, Cohen B, editors. Critical perspectives on racial and ethnic differences in health in late life. Washington, DC: National Academies Press; 2004 [accessed 2018 Nov 2]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK25534/.

2. Krieger N, Williams DR, Moss NE. Measuring social class in US public health research: concepts, methodologies, and guidelines. Annu Rev Public Health 1997;18:341–378.

3. Raju S, Keet CA, Paulin LM, Matsui EC, Peng RD, Hansel NN, et al. Rural residence and poverty are independent risk factors for COPD in the United States. Am J Respir Crit Care Med [online ahead of print] 2 Nov 2018; DOI: 10.1164/rccm.201807-1374OC.

4. Robinson WS. Ecological correlations and the behavior of individuals. Am Sociol Rev 1950;15:351–357.

5. Kreft I, De Leeuw J. Introducing multilevel modeling. Thousand Oaks, CA: SAGE Publications; 1998.

6. Krieger N, Chen JT, Waterman PD, Rehkopf DH, Subramanian SV. Painting a truer picture of US socioeconomic and racial/ethnic health inequalities: the Public Health Disparities Geocoding Project. Am J Public Health 2005;95:312–323.

Copyright © 2019 by the American Thoracic Society

---

Reply to Chandrasekhar

From the Authors:

We thank Dr. Chandrasekhar for her thoughtful comments in response to our recent publication (1). A major goal of our study was to understand the community-level characteristics, such as rural residence and poverty, that contribute to chronic obstructive pulmonary disease (COPD), in addition to describing neighborhoods that face the highest burden of disease. We additionally hope, as Dr. Chandrasekhar has highlighted, that our study brings attention to how researchers can link publicly available datasets to answer questions of significant clinical relevance and develop targeted public health interventions. Dr. Chandrasekhar has raised a number of methodological points that are worthy of consideration in performing such an analysis, regarding 1) the need to use multilevel modeling and 2) the risk of the ecological fallacy.

Dr. Chandrasekhar makes note of the use of multilevel modeling to account for geographical correlation in data structures that take into account neighborhood- and individual-level factors. Although multilevel modeling is frequently used in analyses of geographic factors and disease, this approach requires a significant number of units within each group (census tract in our case) to ensure the stability of the fitting algorithms and to estimate SE. The literature recommends including at least 25 individuals per group for such an analysis, but there were on average only four subjects per census tract (2). As a result, we used standard survey methods in our study, with sample weights and strata provided in the National Health Interview Survey. This accounts for the complex survey design and adjusts the variances for clustering within the sampling unit.

Regarding the risk of the ecologic fallacy, we agree that this represents a potential limitation when census-level characteristics cannot be reduced to the individual level. Our primary goal, however, was to understand the geographic areas with the highest burden of COPD. We ultimately believe that future research should focus on studying COPD in poor, rural areas to better elucidate individual-level effects and characteristics.

We thank Dr. Chandrasekhar for her thoughtful observations. She has raised a number of important points that are worth considering in future analyses that aim to describe the combined impact of neighborhood- and individual-level factors on disease. We hope that our findings pave the way for future investigations into the risk factors for COPD that contribute to health disparities among individuals residing in rural and poor communities.

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

Sarah Raju, M.D., M.P.H.
Corinne A. Keet, M.D., Ph.D.
Laura M. Paulin, M.D., M.H.S.
Elizabeth C. Matsui, M.D., M.H.S.
Roger D. Peng, Ph.D.
Nadia N. Hansel, M.D., M.P.H.
Meredith C. McCormack, M.D., M.H.S.*
Johns Hopkins University
Baltimore, Maryland

*Corresponding author (e-mail: rmccor16@jhmi.edu).

References

1. Raju S, Keet CA, Paulin LM, Matsui EC, Peng RD, Hansel NN, et al. Rural residence and poverty are independent risk factors for COPD in the United States. Am J Respir Crit Care Med [online ahead of print] 2 Nov 2018; DOI: 10.1164/rccm.201807-1374OC.