prevalent cardiovascular disease in men and women: the British Regional Heart Study. *Stroke* 1999;30:841–850.
8. Engström G, Hedblad B, Valind S, Janzon L. Asymptomatic leg and carotid atherosclerosis in smokers is related to degree of ventilatory capacity: longitudinal and cross-sectional results from 'Men born in 1914', Sweden. *Atherosclerosis* 2001;155:237–243.
9. Schroeder EB, Welch VL, Evans GW, Heiss G. Impaired lung function and subclinical atherosclerosis: the ARIC Study. *Atherosclerosis* 2005; 180:367–373.
10. Zureik M, Kauffmann F, Touboul P-J, Courbon D, Ducimetière P. Association between peak expiratory flow and the development of carotid atherosclerotic plaques. *Arch Intern Med* 2001;161: 1669–1676.
11. Alhaj EK, Alhaj NE, Bergmann SR, Hecht H, Matarazzo TJ, Smith S, Alhaj N, Alhaj M, Nelson S. Coronary artery calcification and emphysema. *Can J Cardiol* 2008;24:369–372.
12. Barr RG, Ahmed FS, Carr JJ, Hoffman EA, Jiang R, Kawut SM, Watson K. Subclinical atherosclerosis, airflow obstruction and emphysema: the MESA Lung Study. *Eur Respir J* 2012;39:846–854.
13. Fritz MS, Mackinnon DP. Required sample size to detect the mediated effect. *Psychol Sci* 2007;18:233–239.
14. Bolton CE, Cockcroft JR, Sabit R, Munnery M, McEniery CM, Wilkinson IB, Ebrahim S, Gallacher JE, Shale DJ, Ben-Shlomo Y. Lung function in mid-life compared with later life is a stronger predictor of arterial stiffness in men: the Caerphilly Prospective Study. *Int J Epidemiol* 2009;38:867–876.
15. Zureik M, Benetos A, Neukirch C, Courbon D, Bean K, Thomas F, Ducimetière P. Reduced pulmonary function is associated with central arterial stiffness in men. *Am J Respir Crit Care Med* 2001;164: 2181–2185.
16. Sabit R, Bolton CE, Edwards PH, Pettit RJ, Evans WD, McEniery CM, Wilkinson IB, Cockcroft JR, Shale DJ. Arterial stiffness and osteoporosis in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007;175:1259–1265.
17. Duprez DA, Hearst MO, Lutsey PL, Herrington DM, Ouyang P, Barr RG, Bluemke DA, McAllister D, Carr JJ, Jacobs DR Jr. Associations among lung function, arterial elasticity, and circulating endothelial and inflammation markers: the multiethnic study of atherosclerosis. *Hypertension* 2013;61:542–548.
18. McAllister DA, MacNee W, Duprez D, Hoffman EA, Vogel-Claussen J, Criqui MH, Budoff M, Jiang R, Bluemke DA, Barr RG. Pulmonary function is associated with distal aortic calcium, not proximal aortic distensibility. MESA lung study. *COPD* 2011;8:71–78.
19. Pembroke TPI, Rasul F, Hart CL, Davey Smith G, Stansfeld SA. Psychological distress and chronic obstructive pulmonary disease in the Renfrew and Paisley (MIDSPAN) study. *J Epidemiol Community Health* 2006;60:789–792.
20. Brown LC, Powell JT. Risk factors for aneurysm rupture in patients kept under ultrasound surveillance. UK Small Aneurysm Trial Participants. *Ann Surg* 1999;230:289–296, discussion 296–297.
21. Jackson B, Wright RJ, Kubzansky LD, Weiss ST. Examining the influence of early life socioeconomic position on pulmonary function across the life span: where do we go from here? *Thorax* 2004;59: 186–188.
22. Sun C, Burgner DP, Ponsonby A-L, Saffery R, Huang R-C, Vuillermin PJ, Cheung M, Craig JM. Effects of early-life environment and epigenetics on cardiovascular disease risk in children: highlighting the role of twin studies. *Pediatr Res* 2013;73:523–530.
23. Vestbo J, Anderson J, Brook RD, Calverley PMA, Celli BR, Crim C, Haumann B, Martinez FJ, Yates J, Newby DE. The Study to Understand Mortality and Morbidity in COPD (SUMMIT) study protocol. *Eur Respir J* 2013;41:1017–1022.

Barriers to Understanding the Epidemiology of Noncommunicable Lung Disease in Sub-Saharan Africa

There is growing concern about the current and future burden of noncommunicable lung disease (NCLD) in sub-Saharan Africa (sSA) (1). This is largely driven by recent data documenting the rise of several putative risk factors for NCLD in sSA, including uptake of tobacco and related products (2), exposure to worsening outdoor air pollution from vehicle and industrial emissions (3), and sustained indoor air pollution from the use of biomass fuels for cooking and heating (4). However, empirical evidence of the burden of NCLD, especially spirometry-based general population data, is lacking (Figure 1) (5, 6). This is not entirely surprising, given the limited pulmonary care expertise and clinical capacity in the region (7, 8). Further, most countries in sSA do not routinely collect health data or have vital registration systems (9, 10). As a result, with few exceptions, existing estimates of mortality and morbidity related to NCLD in sSA have been derived from infrequent national or scattered hospital and local surveys, demographic surveillance sites, and extrapolation from statistical models (9, 10). The few attempts to systematically review the burden of NCLD in sSA have primarily assessed chronic obstructive pulmonary disease and have been hampered by heterogeneity in study methods, sample selection, and diagnostic criteria (5, 6, 11, 12).

In this context, the population-based survey of NCLD in Blantyre, Malawi, published in this issue of the *Journal* by Meghji and colleagues (pp. 67–76), provides an informative and needed contribution (13). The authors are to be commended for their efforts to recruit a large study sample from this resource-poor setting and to collect and report data that aligned with the standards of the Burden of Obstructive Lung Disease (BOLD) initiative (14). This work highlights the immense challenges of selecting appropriate sampling designs to facilitate NCLD research in urban sSA. It also raises important questions about the most clinically relevant and informative diagnostic criteria for NCLD in sSA, where participants may be distinctly different from the individuals for whom the gold standard diagnostic standards were derived.

The authors targeted enrollment of 2,000 randomly selected adults from a well-defined sampling district near the central referral hospital in Blantyre (13), enlisting several recruitment tools. These included the assistance of local partners, community engagement teams, and door-to-door enumeration of eligible adults. Yet fieldworkers were unable to locate 531 selected participants, and an additional 192 individuals identified for the study permanently left the area before the study onset.

M.O.H. was supported by the National Institutes of Health (F31HL127947).

Author Contributions: Conception and design: M.O.H.; analysis and interpretation: M.O.H. and D.A.; and drafting the manuscript for important intellectual content: M.O.H. and D.A.

Ultimately, 53% of the initial target of 2,000 adults completed BOLD questionnaires and 37.5% completed acceptable spirometric testing. This lower-than-targeted enrollment, in addition to potentially affecting the authors' statistical analyses, also raises the question of whether the sample that participated in the study is truly representative of the authors' underlying target population of urban Malawian adults. These challenges likely reflect frequent migration and provisional housing situations found in most sSA settings and is a key logistical obstacle that deserves further attention. Developing and piloting local strategies to improve recruitment and retention of subjects, such as financial incentives for research participation, may help future researchers ensure study generalizability and sufficient statistical power.

Several results from the study by Meghji and colleagues warrant discussion in the context of existing data from other countries from sSA (13). Among urban Malawian participants who provided acceptable spirometric measurements, the prevalence of airway obstruction rates using a fixed ratio of $FEV_1/FVC < 70\%$ was 4.3% (males) and 4.1% (females), with airway reversibility present in 4.2% of the cohort. These rates are notably among the lowest spirometry-derived chronic obstructive pulmonary disease estimates to be reported in studies and systematic reviews in sSA (5, 6, 11) (Figure 1). It is notable that there was no association between spirometric results and self-reported respiratory symptoms. Further, in contrast to previous reports, the authors did not find a measureable association between airway obstruction and exposure to biomass or tobacco use (5, 11, 12). More studies are needed to explain the observed variability in NCLD prevalence and risk between countries in sSA, including exploration of novel exposures and long-term health consequences of spirometric abnormalities.

To estimate the prevalence of moderate-to-severe obstruction and spirometric restriction, Meghji and colleagues used and compared two distinct populations as reference values (13). In the first analysis, they applied age-, sex-, and height-standardized predicted values from the third survey wave of the National Health and Nutrition Examination Survey (NHANES III), derived from Caucasians in the United States (13). In the second analysis, they used locally derived reference ranges from nonsmoking, asymptomatic participants in the study (13). The use of different reference ranges limitedly altered the prevalence estimates of moderate-to-severe obstruction (NHANES = 3.6%; locally derived = 2.3%). In contrast, the prevalence of restriction differed by 29.6%, depending on the reference ranges used (NHANES = 38.6% vs. locally derived = 9.0%). The authors propose reasonable explanations for the difference in estimates, such as ethnic variation in lung size and anthropometry, the latter of which is well documented in analyses of NHANES III data (15). As the "correct" reference population remains debatable, it may be informative to also compare the Malawian population with the African-American participants in NHANES III (15). Given the human and financial costs of misdiagnosis, development of a case definition of obstructive and restrictive lung disease that is adaptable to diverse global populations is a public health priority (6, 16, 17).

In conclusion, the work by Meghji and colleagues demonstrates the operational challenges to conducting high-quality NCLD research in a low-resource urban sSA setting (13). The authors' success in conducting a standardized BOLD study protocol highlights the positive and continued influence of the BOLD initiative in guiding comparable and population-based research data in sSA (14, 16). The findings of this research reinforce the need for future longitudinal studies that can validate spirometry

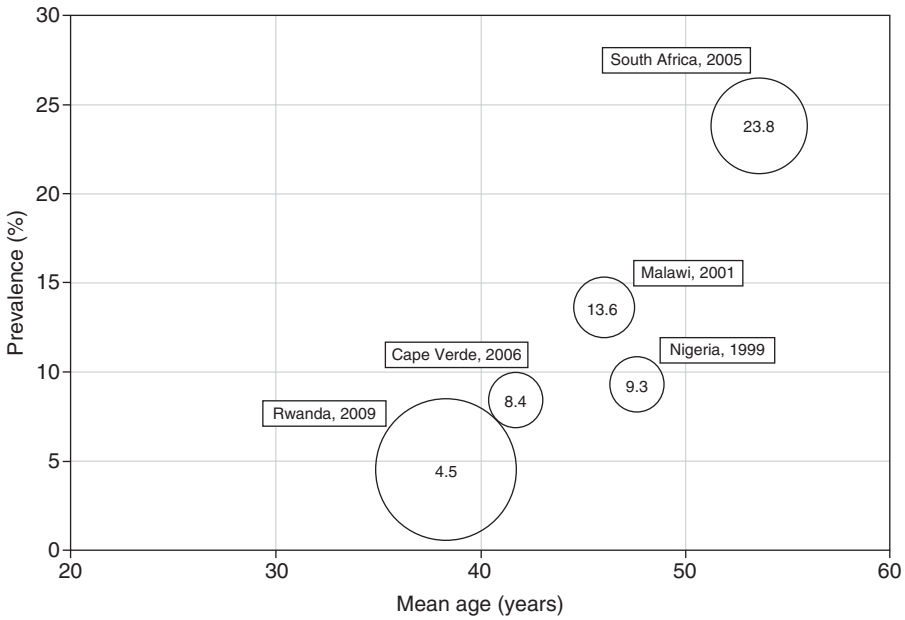

Figure 1. Distribution of spirometry-derived chronic obstructive pulmonary disease (COPD) prevalence rates in five sub-Saharan Africa (sSA) studies. This figure reports the mean age- and spirometry-derived COPD prevalence rates in five population-based studies in sSA identified in a systematic review covering the period from 1990 to 2014 (6). Information about the study sample and design of each study is summarized in the review. The size of the bubble corresponds to the relative sample size of the study. The year reported for each study is the time (or midpoint) of the study, not the year of publication.

metrics in diverse populations, provide greater clarity about modifiable exposures for NCLD, and explore the long-term health outcomes of NCLD in resource-poor settings (18). As we await data from these future studies, consortiums such as the BOLD initiative will continue to improve local health infrastructures and medical provider knowledge and remain critical to advancing our knowledge of the global burden of NCLD (7, 8, 14, 16, 19). ■

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

Michael O. Harhay, M.P.H.
Perelman School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

Davies Adeloye, M.D., Ph.D.
Demography and Social Statistics
Covenant University
Ota, Nigeria
and
Centre for Global Health Research
University of Edinburgh
Edinburgh, United Kingdom

References

1. Kontis V, Mathers CD, Bonita R, Stevens GA, Rehm J, Shield KD, Riley LM, Poznyak V, Jabbour S, Garg RM, *et al*. Regional contributions of six preventable risk factors to achieving the 25 × 25 non-communicable disease mortality reduction target: a modelling study. *Lancet Glob Health* 2015;3:e746–e757.
2. Ng M, Freeman MK, Fleming TD, Robinson M, Dwyer-Lindgren L, Thomson B, Wollum A, Sanman E, Wulf S, Lopez AD, *et al*. Smoking prevalence and cigarette consumption in 187 countries, 1980-2012. *JAMA* 2014;311:183–192.
3. Dieter S. Review of urban air quality in Sub-Saharan Africa region - air quality profile of SSA countries. Washington, DC: World Bank; 2012 [accessed 2016 Jan 26]. Available at: http://documents.worldbank.org/curated/en/2012/03/16193871/review-urban-air-quality-sub-saharan-africa-region-air-quality-profile-ssa-countries
4. Gordon SB, Bruce NG, Grigg J, Hibberd PL, Kurmi OP, Lam KB, Mortimer K, Asante KP, Balakrishnan K, Balmes J, *et al*. Respiratory risks from household air pollution in low and middle income countries. *Lancet Respir Med* 2014;2:823–860.
5. Adeloye D, Basquill C, Papana A, Chan KY, Rudan I, Campbell H. An estimate of the prevalence of COPD in Africa: a systematic analysis. *COPD* 2015;12:71–81.
6. Adeloye D, Chua S, Lee C, Basquill C, Papana A, Theodoratou E, Nair H, Gasevic D, Sridhar D, Campbell H, *et al*.; Global Health Epidemiology Reference Group (GHERG). Global and regional estimates of COPD prevalence: systematic review and meta-analysis. *J Glob Health* 2015;5:020415.
7. Obaseki D, Adeniyi B, Kolawole T, Onyedum C, Erhabor G. Gaps in capacity for respiratory care in developing countries: Nigeria as a case study. *Ann Am Thorac Soc* 2015;12:591–598.
8. Chakaya JM, Carter EJ, Hopewell PC. Pulmonary specialty training to improve respiratory health in low- and middle-income countries: needs and challenges. *Ann Am Thorac Soc* 2015;12:486–490.
9. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015;386:743–800.
10. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015;385:117–171.
11. Finney LJ, Feary JR, Leonardi-Bee J, Gordon SB, Mortimer K. Chronic obstructive pulmonary disease in sub-Saharan Africa: a systematic review. *Int J Tuberc Lung Dis* 2013;17:583–589.
12. van Gemert F, van der Molen T, Jones R, Chavannes N. The impact of asthma and COPD in sub-Saharan Africa. *Prim Care Respir J* 2011; 20:240–248.
13. Meghji J, Nadeau G, Davis KJ, Wang D, Nyirenda MJ, Gordon SB, Mortimer K. Noncommunicable lung disease in sub-Saharan Africa: a community-based cross-sectional study of adults in urban Malawi. *Am J Respir Crit Care Med* 2016;194:67–76.
14. Buist AS, Vollmer WM, Sullivan SD, Weiss KB, Lee TA, Menezes AM, Crapo RO, Jensen RL, Burney PG. The Burden of Obstructive Lung Disease Initiative (BOLD): rationale and design. *COPD* 2005;2: 277–283.
15. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999;159:179–187.
16. Lamprecht B, Soriano JB, Studnicka M, Kaiser B, Vanfleteren LE, Gnatiuc L, Burney P, Miravitlles M, García-Rio F, Akbari K, *et al*.; BOLD Collaborative Research Group; EPI-SCAN Team; PLATINO Team; PREPOCOL Study Group. Determinants of underdiagnosis of COPD in national and international surveys. *Chest* 2015;148: 971–985.
17. van Dijk WD, Gupta N, Tan WC, Bourbeau J. Clinical relevance of diagnosing COPD by fixed ratio or lower limit of normal: a systematic review. *COPD* 2014;11:113–120.
18. Dalal S, Beunza JJ, Volmink J, Adebamowo C, Bajunirwe F, Njelekela M, Mozaffarian D, Fawzi W, Willett W, Adami HO, *et al*. Non-communicable diseases in sub-Saharan Africa: what we know now. *Int J Epidemiol* 2011;40:885–901.
19. World Health Organization. Global Alliance against Chronic Respiratory Diseases 2014 General Meeting Report. Geneva, Switzerland: WHO Press; 2014.

Galectin-3: Distant Biomarker or Relevant Target?

There have been significant advances in our understanding of the pathogenesis of idiopathic pulmonary fibrosis (IPF) in the last decade. These advances have led to the availability of two approved drugs for the treatment of a disease that is universally fatal (1, 2). A major challenge is the early identification of patients who will derive the most benefit from these treatment options. Biomarker and genetic studies suggest there are a variety of phenotypes within the generic label of IPF. Large-scale genetic studies have identified MUC5B and telomerase mutations as important predictors of disease susceptibility (3). Other studies have attempted to identify biomarkers in peripheral blood that might predict disease progression or behavior (4, 5).

In this issue of the *Journal*, Ho and colleagues (pp. 77–83) have added some interesting insights into the pathogenesis of