

7. Bero L, Chartres N, Diong J, Fabbri A, Ghersi D, Lam J, *et al.*. The risk of bias in observational studies of exposures (ROBINS-E) tool: concerns arising from application to observational studies of exposures. *Syst Rev* 2018;7:242.
8. Hill AB. The environment and disease: association or causation? *Proc R Soc Med* 1965;58:295–300.
9. Fedak KM, Bernal A, Capshaw ZA, Gross S. Applying the Bradford Hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology. *Emerg Themes Epidemiol* 2015;12:14.
10. Hume D. A treatise on human nature. London: Clarendon Press; 1739.
11. Gershon AS, Jafarzadeh SR, Wilson KC, Walkey AJ. Clinical knowledge from observational studies everything you wanted to know but were afraid to ask. *Am J Respir Crit Care Med* 2018;198:859–867.
12. Ioannidis JPA. Contradicted and initially stronger effects in highly cited clinical research. *JAMA* 2005;294:218–228.
13. MacMahon S, Collins R. Reliable assessment of the effects of treatment on mortality and major morbidity, II: observational studies. *Lancet* 2001;357:455–462.
14. Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovich C, Song F, *et al.*; International Stroke Trial Collaborative Group; European Carotid Surgery Trial Collaborative Group. Evaluating non-randomised intervention studies. *Health Technol Assess* 2003;7:iii–x, 1–173.
15. Bosco JLF, Silliman RA, Thwin SS, Geiger AM, Buist DSM, Prout MN, *et al.* A most stubborn bias: no adjustment method fully resolves confounding by indication in observational studies. *J Clin Epidemiol* 2010;63:64–74.
16. Vandembroucke JP. When are observational studies as credible as randomised trials? *Lancet* 2004;363:1728–1731.
17. Vandembroucke JP. Why do the results of randomised and observational studies differ? *BMJ* 2011;343:d7020.
18. Sox HC, Greenfield S. Comparative effectiveness research: a report from the Institute of Medicine. *Ann Intern Med* 2009;151:203–205.

stand by this framework for decision-making but acknowledge the need to update the framework as new evidence emerges. ■

**Author disclosures** are available with the text of this letter at [www.atsjournals.org](http://www.atsjournals.org).

Andrea S. Gershon, M.D., M.Sc.\*  
Sunnybrook Health Sciences Centre  
Toronto, Ontario, Canada  
and

University of Toronto  
Toronto, Ontario, Canada

Peter K. Lindenauer, M.D., M.Sc., M.H.M.  
University of Massachusetts Medical School–Baystate  
Springfield, Massachusetts

Jerry A. Krishnan, M.D., Ph.D.†  
University of Illinois at Chicago  
Chicago, Illinois

On behalf of all the authors

ORCID IDs: 0000-0002-0246-594X (A.S.G.); 0000-0002-8414-0507 (P.K.L.); 0000-0001-5525-4778 (J.A.K.).

\*Corresponding author (e-mail: [andrea.gershon@ices.on.ca](mailto:andrea.gershon@ices.on.ca)).

†J.A.K. is Associate Editor of *AJRCCM*. His participation complies with American Thoracic Society requirements for recusal from review and decisions for authored works.

Copyright © 2021 by the American Thoracic Society



## Reply to Albert

From the Authors:

We thank Dr. Albert for the comments about our ATS Research Statement (1). We agree that well-performed randomized clinical trials (RCTs) can produce high-quality evidence for making inferences about the causal effects of an intervention on outcomes. However, for most cases, evidence from high-quality RCTs for outcomes that are critical to decision-making does not exist or is insufficient for informing a course of action with confidence. For example, of 19 guideline recommendations in the recently published 2020 asthma guideline update from the National Asthma Education and Prevention Program, only 3 were based on high-quality evidence (2). The ATS Research Statement explains the framework proposed by the Grading of Recommendations Assessment, Development and Evaluation working group in cases in which there is insufficient evidence from RCTs. We

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

The authors are the co-chairs of the official American Thoracic Society Document Informing Health Care Decisions with Observational Research Assessing Causal Effect: An Official ATS Research Statement.

Originally Published in Press as DOI: 10.1164/rccm.202104-0851LE on June 3, 2021

## References

1. Gershon AS, Lindenauer PK, Wilson KC, Rose L, Walkey AJ, Sadatsafavi M, *et al.* Informing healthcare decisions with observational research assessing causal effect. An official American Thoracic Society Research Statement. *Am J Respir Crit Care Med* 2021;203:14–23.
2. Cloutier MM, Baptist AP, Blake KV, Brooks EG, Bryant-Stephens T, DiMango E, *et al.*; Expert Panel Working Group of the National Heart, Lung, and Blood Institute (NHLBI) administered and coordinated National Asthma Education and Prevention Program Coordinating Committee (NAEPPCC). 2020 focused updates to the Asthma Management Guidelines: a report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. *J Allergy Clin Immunol* 2020;146:1217–1270.

Copyright © 2021 by the American Thoracic Society



## Multiple Manifestations of Systemic Sclerosis Affect Walk Distance

To the Editor:

We welcome the novel report on the efficacy of B-cell depletion in the treatment of pulmonary arterial hypertension (PAH) associated with

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

Originally Published in Press as DOI: 10.1164/rccm.202104-0938LE on June 9, 2021