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Dear Dr. Schisterman,
We are submitting our manuscript titled "**Scenarios for feedback loop failure in medical diagnosis**" by doctoral candidate Rachael C. Aikens, Jonathan H Chen, MD, PhD, Michael Baiocchi, PhD, Julia F Simard, ScD for consideration as an original contribution in *American Journal of Epidemiology*.

We recently published a Research Letter in *AJE* where we studied whether cognitive bias in clinical decision-making might contribute to diagnostic delays and/or missed diagnoses resulting in sex disparities in outcomes using 5 clinical case vignettes in a randomized survey of 296 rheumatologists. We noted that the proportion correctly diagnosed with systemic lupus (SLE) was commensurate with the evidence base (e.g. less likely to diagnose SLE in White males), suggesting cognitive and implicit biases might contribute to delayed or missed diagnoses in cases that do not look like "the average". The present work further builds upon this.

Our premise is that cognitive heuristic shortcuts in clinical decision-making influence how clinicians diagnose, which feeds into the future evidence base. Cognitive biases in clinical decision making may unintentionally contribute to disparities. To a patient, medical diagnosis can be the gateway to essential care. Across a population, the diagnostic process shapes medical research from observational studies to bench science. But the diagnostic process is a selective one depending on a person's symptoms, their willingness and ability to seek care, and their clinician's judgment synthesizing medical history, risk factors, and presentation with an evolving evidence base.

A *feedback loop failure* may occur if misleading "evidence" about disease etiology encourages systematic errors in the diagnostic process in a way that self-perpetuates or self-exacerbates, compromising patient care. This paper defines scenarios for feedback loop failure in medical diagnosis. Through simulated case-studies, we characterize how disease incidence, presentation, and risk factors may be misunderstood when observational data are summarized naive to the diagnostic selection process. We conclude that direct summaries based on diagnosed individuals may be misleading, especially concerning those symptoms and risk factors which influence the diagnostic process itself.

We affirm that the manuscript has not been submitted nor is simultaneously being submitted elsewhere, is not at the time of submission under consideration by another journal or other publication, and that no portion of the data has been or will be published elsewhere while the manuscript is under review by the journal, unless rejected by the *American Journal of Epidemiology* or withdrawn. We affirm that no portion of the data has been or will be published elsewhere while the manuscript is under review by *American Journal of Epidemiology*. JFS, RCA, and MB designed this study. RCA implemented the simulated case studies and generated the figures and supplementary material. All authors contributed to the interpretation of results and the writing of all sections of the manuscript (including tables 1, 3, and 4).

Thank you for your consideration.

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