

1 **Response to Letter to the Editor From Nelson et al: "Understanding the link between obesity and severe**  
2 **COVID-19 outcomes: Causal mediation by systemic inflammatory response"**

3 *Authors and affiliations:*

4 Andrea S Foulkes, ScD<sup>1,2,3,\*</sup> afoulkes@mgh.harvard.edu

5 Caitlin Selvaggi, MS<sup>1</sup> cselvaggi@mgh.harvard.edu

6 Daniel Shinnick, BS<sup>1</sup> DSHINNICK@mgh.harvard.edu

7 Heidi Lumish, MD<sup>4</sup> hel2010@nyp.org

8 Tingyi Cao, BS<sup>1,3</sup> tingyi\_cao@hsph.harvard.edu

9 Tanayott Thaweethai, PhD<sup>1,2</sup> tthaweethai@mgh.harvard.edu

10 Jing Qian, PhD<sup>5</sup> qian@schoolph.umass.edu

11 James B Meigs, MD<sup>2</sup> jmeigs@mgh.harvard.edu

12 Virginia A Triant, MD, MPH<sup>2</sup> vtriant@mgh.harvard.edu

13 Ingrid V Bassett, MD, MPH<sup>2</sup> ibassett@mgh.harvard.edu

14 Muredach P Reilly, MBBCh, MSCE<sup>4,6</sup> mpr2144@cumc.columbia.edu

15

16 *Corresponding Author:* Andrea S Foulkes, 50 Staniford Street, Boston, MA 02114 USA,

17 afoulkes@mgh.harvard.edu, Tele: +1 (617) 724-8208. ORCID ID 0000-0002-9520-0501. <sup>1</sup>Biostatistics,

18 Massachusetts General Hospital, Boston, MA USA; <sup>2</sup>Department of Medicine, Harvard Medical School;

19 <sup>3</sup>Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA USA; <sup>4</sup>Division of

20 Cardiology, Columbia University, New York, NY USA; <sup>5</sup>Biostatistics and Epidemiology, University of

21 Massachusetts, Amherst, MA USA; <sup>6</sup>Irving Institute for Clinical and Translational Research, Columbia

22 University.

23

24 *Competing interests:* The authors declare no competing financial interests

25

26 *Disclosure statement:* The authors have nothing to disclose.

27

28 **Keywords:** Biomarkers, COVID-19, inflammation, obesity, sex, SARS-CoV-2, mediation

29

30

1 We agree fully with Nelson et al. [1] that rigor in the analysis of sex is critically important in studies of severe  
2 outcomes associated with SARS-CoV-2 infection, and particularly in investigations of obesity, inflammation,  
3 and the mechanistic underpinnings of severe disease. Indeed, in tandem to the article in JCEM [2], members of  
4 our team published a manuscript specifically investigating biomarkers of cardiac injury, renal injury, and  
5 inflammation as potential mediators of sex-associated mortality among SARS-CoV-2 infected individuals [3]. In  
6 other work, we report sex stratified analyses in the study of signature biomarker states and mortality [4] and  
7 characterize sex differences in inflammatory markers among patients hospitalized with SARS-CoV-2 [5].  
8 Appropriate handling of sex as a potential moderator or confounder is of paramount importance and for over a  
9 decade, we have included this focus in our clinical and translational research e.g., [6,7]. We thank Nelson et al  
10 for highlighting this need which we may have underemphasized in [2] as we were undertaking a much more  
11 comprehensive sex-specific analysis [3]. Notably this second paper is published within the Section on Sex and  
12 Gender in Cardiovascular Medicine, focused specifically on examining sex differences in outcomes.  
13 Importantly, we do want to clarify that, in our JCEM manuscript [2], models were adjusted for sex and this fact  
14 was indicated throughout [see paragraph 2 of Statistical Methods, legend to Figure 1, footnote b of Table 2 and  
15 footnote b of Table 3]. We fully endorse the SAGER guidelines [8] and concur unequivocally with Nelson et al  
16 that “Science needs to follow scientific principles and guidelines, especially when not following them introduces  
17 sex and gender bias”.

18

## 19 **References**

- 20 [1] Kaitlin Nelson; Jerilynn C. Prior; Dharani Kalidasan; Cara Tannenbaum; Sonia Shirin; Claudie Berger;  
21 Azita Goshtasebi, Letter to the Editor from Nelson et al: “Understanding the Link Between Obesity and  
22 Severe COVID-19 Outcomes: Causal Mediation by Systemic Inflammatory Response.”
- 23 [2] Foulkes AS, Selvaggi C, Shinnick D, Lumish H, Kim E, Cao T, Thaweethai T, Qian J, Lu F, Yan J, Cheng  
24 D, He W, Clerkin KJ, Madhavan MV, Meigs JB, Triant VA, Lubitz SA, Gupta A, Bassett IV, Reilly MP.  
25 Understanding the Link Between Obesity and Severe COVID-19 Outcomes: Causal Mediation by Systemic  
26 Inflammatory Response. *J Clin Endocrinol Metab.* 2022 Jan 18;107(2):e698-e707. doi:  
27 10.1210/clinem/dgab629. PMID: 34473294; PMCID: PMC8499919.
- 28 [3] Lumish HS, Kim E, Selvaggi C, Cao T, Gupta A, Foulkes AS, Reilly MP. Biomarkers of Cardiac Injury,  
29 Renal Injury, and Inflammation Are Strong Mediators of Sex-Associated Death in COVID-19. *Front*  
30 *Cardiovasc Med.* 2022 Apr 25;9:809997. doi: 10.3389/fcvm.2022.809997. PMID: 35548417; PMCID:  
31 PMC9081502.
- 32 [4] Selvaggi C, Harrison LJ, Kim E, Reilly MP, Foulkes AS. Signature biomarker states and mortality among  
33 hospitalized SARS-CoV-2-infected patients. *J Nephrol.* 2022 Apr;35(3):765-767. doi: 10.1007/s40620-021-  
34 01239-z. Epub 2022 Jan 6. PMID: 34989977; PMCID: PMC8733911.
- 35 [5] Lau ES, McNeill JN, Paniagua SM, Liu EE, Wang JK, Bassett IV, Selvaggi CA, Lubitz SA, Foulkes AS, Ho  
36 JE. Sex differences in inflammatory markers in patients hospitalized with COVID-19 infection: Insights  
37 from the MGH COVID-19 patient registry. *PLoS One.* 2021 Apr 28;16(4):e0250774. doi:  
38 10.1371/journal.pone.0250774. PMID: 33909684; PMCID: PMC8081177.
- 39 [6] Ferguson JF, Patel PN, Shah RY, Mulvey CK, Gadi R, Nijjar PS, Usman HM, Mehta NN, Shah R, Master  
40 SR, Probert KJ, Reilly MP. Race and gender variation in response to evoked inflammation. *J Transl Med.*  
41 2013 Mar 12;11:63. doi: 10.1186/1479-5876-11-63. PMID: 23497455; PMCID: PMC3636014.
- 42 [7] Lumish HS, O'Reilly M, Reilly MP. Sex Differences in Genomic Drivers of Adipose Distribution and  
43 Related Cardiometabolic Disorders: Opportunities for Precision Medicine. *Arterioscler Thromb Vasc Biol.*  
44 2020 Jan;40(1):45-60. doi: 10.1161/ATVBAHA.119.313154. Epub 2019 Nov 21. PMID: 31747800.
- 45 [8] Heidari S, Babor TF, De Castro P, Tort S, Curno M. Sex and Gender Equity in Research: rationale for the  
46 SAGER guidelines and recommended use. *Res Integr Peer Rev.* 2016 May 3;1:2. doi: 10.1186/s41073-016-  
47 0007-6. PMID: 29451543; PMCID: PMC5793986.

48

49