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EDITORIAL

Understanding gender disparities in outcomes after sepsis

M. Elizabeth Wilcox[1,2*], John P. Donnelly[3,4] and Nazir I. Lone[5,6]

It is assumed that medicine treats patients based primarily on their physical illnesses. Sociologic attributes such as religion, nationality, economic class, and gender might inform patient values, but should not negatively affect care. A number of studies, however, suggest that a patient's sex may influence both the provision of care as well as outcomes. Critical care is not immune to such bias.

In this issue of *Intensive Care Medicine*, Sunden-Cullberg et al. [1] in a nationwide cohort study of adults ($n = 2720$) with severe sepsis or septic shock, report that women are less likely to receive all items in a 1-h emergency department sepsis care bundle compared with men. Overall mortality rates were similar for men (23.1%) and women (25.0%), but after adjustment, women had 1.3-fold higher odds of death at 30-days following an ICU admission (3% absolute difference). The authors go on to report that emergency medical services were more likely to record vital signs and provide intravenous (iv) fluids as well as oxygen therapy to men as compared to women with sepsis [1]. In the emergency department (ED), men were more likely to not only receive iv antibiotics, but also receive them more expeditiously (by approximately 20 min) as compared to women [1].

A number of limitations to the study design, that the authors acknowledge, suggest that readers must treat the results with caution. Firstly, the authors only had access to data for patients who presented with sepsis in the ED and were then subsequently admitted to ICU. In European EDs, only 1 in 3 patients fulfilling sepsis criteria (and therefore eligible for bundle compliance) were admitted to ICU [2]. This potential source of selection bias means that we can only evaluate the relationship between sex and bundle compliance in a minority of eligible patients (Fig. 1). Secondly, the reported association between sex and mortality could be mediated by a range of additional unmeasured factors. Whilst several key variables were included in the primary analysis, the addition of important factors such as infection source and comorbidities rendered the association non-significant. In addition, the authors adjusted for post- rather than pre-resuscitation physiology. The mediation analysis demonstrated that the association between sex and mortality cannot be explained by poorer quality care (measured by bundle completion), raising further doubts about the excess mortality demonstrated.

Gender differences have been documented in processes of care across the trajectory of ICU care. In an ICU, men on average consistently use more resources per admission and impose higher nurse workloads [3].These differences have been documented consistently across diagnostic subgroups, including sepsis, multiple trauma, chronic obstructive pulmonary disease, acute respiratory distress syndrome, pneumonia, and cardiac arrest [3]. Further, women are less likely than men to receive advanced life support measures such as mechanical ventilation, despite similar illness severity [4]. Such variation in care limitations could stem from less aggressive treatment preferences by women (or their surrogates) [5], as women tend to be younger when admitted to the ICU as compared to their spouses. Due to their longer life expectancy and to their children more likely acting as surrogate decision makers, (as opposed to men whose wives typically act as surrogates) it is possible that women's wishes are more often misperceived during critical illness [6]. Interestingly, physician–patient communication regarding preferences for aggressiveness of care has been deemed suboptimal with women in a large

*Correspondence: elizabeth.wilcox@utoronto.ca
[1] Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, ON, Canada
Full author information is available at the end of the article

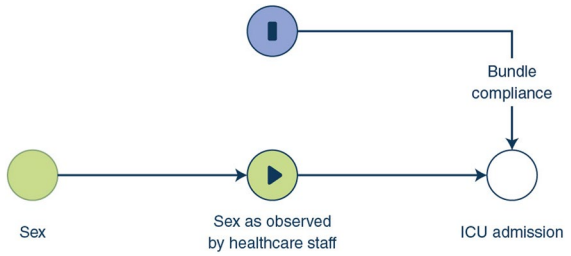

Fig. 1 Casual diagram demonstrating the selection bias which might arise through restricting the cohort to patients admitted to ICU. The diagram is simplified and drawn under the null hypothesis: no casual relationship between sex (as observed by healthcare staff) and bundle compliance. By restricting the cohort to those subsequently admitted to ICU (conditioning on a 'collider'), 'a black door path' is opened between sex and bundle compliance. This selection can result in an apparent association being observed between sex and bundle compliance when none exists

multicentre observational study [7], a finding that is more pronounced when women are of older age [8].

Such gender disparities have been known to exist for decades in other patient populations. For example, women with myocardial infarction receive less guideline-based diagnoses and less invasive treatment than men [9]. Further, women with heart failure receive fewer guideline-based diagnostic procedures, treatments, device implantations and transplants [10]. These gender differences persist even after considering factors that may explain variation in care such as comorbidities, presentation, appropriateness of treatment, and patient preferences, thus suggesting the differences represent true disparities. In a systematic review, Fitzgerald and Hurst report that healthcare professionals exhibit implicit biases that lead to a negative evaluation of a person on the basis of irrelevant characteristics such as race or gender [11]. More research in clinical care settings and a greater homogeneity in methods employed to test implicit biases in healthcare is needed.

Change is historically slow. Until relatively recently the prevailing scientific tradition was to exclude women from clinical trials. The first trial testing the effect of estrogen on secondary prevention of coronary heart disease, published in *The Journal of the American Medical Association* in 1973, enrolled 8341 men and no women [12]. Major reasons accounting for the exclusion of women and, even when women were included excluding their data, were: (1) potential reproductive risk of participation, (2) misperceptions that women are less affected by certain disorders or health conditions and, when affected, would respond to the same treatment, and (3) the perception that women added more complexity to trials and thus increased cost and need for greater analytic capacity of scientific design [13]. Despite such protectionist perspectives now viewed as discriminatory and lacking scientific merit, ongoing unconscious biases must be recognized and tempered to remedy their effects on sound scientific inquiry. The implementation of consensus requirements for change have provided much needed momentum.

The study by Sunden-Cullberg et al. reminds us that the pursuit for gender equality in healthcare might extend to critical care, demanding sound surveillance for existing disparities in clinical practice as well as future research endeavours. Despite significant methodological limitations, this paper contributes to the relatively understudied literature of gender in critical care. The provocative findings from Sunden-Cullberg et al. need to be replicated in a more robustly designed study to specifically address the aforementioned limitations. Further, we would argue that movement forward in gender equality studies should also include a concerted effort for medical databases to capture non-binary gender patients. Such patients might be hypothesized to endure especially unique social pressures that influence their care.

Author details
[1] Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, ON, Canada. [2] Division of Respirology, Department of Medicine, University Health Network and Mount Sinai Hospital, Toronto, ON, Canada. [3] Department of Learning Health Sciences, University of Michigan, Ann Arbor, MI, USA. [4] Institute for Healthcare Policy & Innovation, University of Michigan, Ann Arbor, MI, USA. [5] Usher Institute, University of Edinburgh, Edinburgh, UK. [6] Department of Critical Care, Royal Infirmary of Edinburgh, NHS Lothian, Edinburgh, UK.

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Compliance with ethical standards

Conflicts of interest
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