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REVIEW ARTICLE

Evidence-Based Emergency Medicine

Crucial considerations: Sex differences in the epidemiology, diagnosis, treatment, and outcomes of acute pulmonary embolism in non-pregnant adult patients

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Abstract

Acute pulmonary embolism (PE) affects over 600,000 Americans per year and is a common diagnostic consideration among emergency department patients. Although there are well-documented differences in the diagnosis, treatment, and outcomes of cardiovascular conditions, such as ischemic heart disease and stroke, the influence of sex and gender on PE remains poorly understood. The overall age-adjusted incidence of PE is similar in women and men, but women have higher relative rates of PE during early and mid-adulthood (ages 20–40 years); whereas, men have higher rates of PE after age 60 years. Women are tested for PE at far higher rates than men, yet women who undergo computed tomography pulmonary angiography are ultimately diagnosed with PE 35%–55% less often than men. Among those diagnosed with PE, women are more likely to have severe clinical features, such as hypotension and signs of right ventricular dysfunction. When controlled for PE severity, women are less likely to receive reperfusion therapies, such as thrombolysis. Finally, women have more bleeding complications for all types of anticoagulation. Further investigation of possible sex-specific diagnostic and treatment algorithms is necessary in order to more accurately detect and treat acute PE in non-pregnant adults.

KEYWORDS

acute right ventricular failure, anticoagulation, diagnostics, epidemiology, health equity, pulmonary embolism, sex differences, sex and gender, thromboembolism, thrombosis

1 | INTRODUCTION

Both biological sex and gender identity are important determinants of health. Decades ago, biological sex was found to be an important modulator of ischemic heart disease,[1] and since that time sex and gender have proven to be of critical importance in understanding a number of cardiovascular disease processes, including acute coronary syndrome,[2] heart failure,[3,4] arrhythmias,[1] and Takotsubo cardiomyopathy.[5] Many sex-based differences are rooted in neurohormonal effects, particularly those of estrogenic compounds, and one of the most well-established risk factors for the development of an acute pulmonary embolism (PE) is the administration of exogenous estrogens.[6,7] Biological sex, and concomitantly sex hormones, therefore play a scientifically plausible role in the pathogenesis,

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diagnosis, and treatment of pulmonary embolism. PE is the third leading cardiovascular cause of death in the United States, yet the influence of patients' sex on PE incidence, severity, and treatment is not well understood.[8] Even less is known about gender-related risk factors, such as smoking, exercise patterns, or obesity, which likely play a role in each individual's risk profile. This structured review examines current knowledge around the impact of biological sex and the degree to which any disparities exist in the evaluation and treatment of acute PE.

Acute PE affects over 600,000 patients annually in the United States.[9] It is a common consideration in emergency department (ED) patients, as chest pain and shortness of breath are 2 of the top 5 most common chief complaints among ED patients and together represent over 10 million annual visits.[10] PE is considered a potentially life-threatening diagnosis in these patients. The diagnostic evaluation for PE, however, is at once complex, time consuming, expensive, and potentially harmful to patients when not applied judiciously. In the current era of increasingly precise evidence-based medicine, finding the balance between potential harms of overtesting and benefits of diagnosis is critical to accurately identify individuals with PE. As such, we have collated the best available evidence on sex differences in the epidemiology, presentation, diagnosis, and management of PE to aid emergency physicians in more accurately and precisely diagnosing and managing PE in non-pregnant patients. We also highlight areas of focus for future research to more fully elucidate the role of sex in acute PE.

Biological sex refers to one's chromosomal, hormonal, and gonadal sex and the physiology associated with these. Gender, in contrast, is the sociocultural aspect of one's identity as man or woman. The terms "woman" and "female" and "man" and "male" are used interchangeably in the text, but in each case refer to biological sex, as this is the focus of the available literature; in the cases in which gender is discussed separately, this is denoted in the text. Given the lack of available data regarding intersex and non-binary genders, these are not addressed but are recognized as an important area of future research.

2 | METHODS

This structured review was conducted using multiple search strategies to identify research of interest. A comprehensive literature review was conducted in the National Library of Medicine database PubMed®, using the validated sex and gender search tool.[11] This search tool was derived to enable researchers to easily access sex- and gender-specific work, even if those terms were not included in the title. The initial search was conducted on October 26, 2020, and search terms were as follows: pulmonary embolism and (sex based OR sex factors OR sex distribution OR sex characteristics OR sex dimorphism OR gender difference* OR gender based) AND (gender[ti] OR sex[ti] OR women[ti] OR female[ti]) AND (Humans[Mesh] AND English[lang]). This initial search yielded 88 results that were reviewed for inclusion. Manuscripts were included if they provided any primary data on sex differences in any aspect of PE. Manuscripts published before 2000 were excluded, given that the diagnosis, management, and prognosis of acute PE have changed significantly since that time. All non-primary research was excluded; this included letters to the editor, commentaries, case reports, and non-systematic reviews. Finally, manuscripts specific to venous thromboembolism (VTE)/PE in pregnancy were excluded, given that they are beyond the scope of this review. Of those identified and reviewed by this search strategy, 42 manuscripts met inclusion criteria and were reviewed in detail (see Appendix Table 1). Several studies met inclusion criteria but were of minimal relevance, quality, or small size and thus are not discussed in text. Levels of evidence were not included in Appendix Table 1, as the majority of the included studies were classified as level 3 evidence (cohort, cross-sectional studies) by the Oxford Centre for Evidence Based Medicine Guidelines.[12]

In addition, the authors reviewed the references of included works to ensure an exhaustive search. These references are cited in text, as appropriate. Finally, many of the large clinical trials on PE were reviewed by hand to evaluate for any sex-specific or sex stratified data, even if sex differences were not the focus of the investigation.

2.1 | Epidemiology

The age-adjusted incidence of PE in the general adult population is reported to be between 29 and 109 cases per 100,000 person-years.[13–18] The wide range reflects differences in data sources and study designs, as well as the variation in age-adjusted rates from using different standard populations. Beyond those methodological factors, assessment of the true incidence of PE is complicated by large numbers of asymptomatic cases,[19,20] instances of sudden unexplained death caused by, but not attributed to PE,[21,22] and a lack of effective epidemiologic surveillance.[23] Furthermore, the reported incidence of PE has nearly tripled since the late 1980s following the introduction of highly sensitive D-dimer assays and computed tomographic pulmonary angiography (CTPA) that detect increasing numbers of potentially clinically insignificant small emboli or produce false-positive results.[19,24]

PE is primarily a disease of the elderly. The incidence of the disease doubles every decade after age 40,[15] increasing from ≈10 cases/person-year among patients aged 20–29 years to 246 cases/person-year among patients aged 80 years and older.[25] Although there is no clear sex difference in overall age-adjusted incidence of PE, men and women have different patterns of PE incidence as they age.[13,15,26] Among patients between 20 and 40 years of age, women develop PE at a rate that is roughly twice that of men (eg, ≈16 vs 7 cases per 100,000 person years).[15,27] Between 60 and 80 years of age, however, PE incidence is ≈20%–25% higher in men compared to women.[28] Emerging data suggest that these epidemiologic trends may vary among special populations, such as those with heart failure and antiphospholipid syndrome; however, these data have not yet been replicated.[29–31]

There are a number of well-established risk factors for PE, which include major trauma, surgery, cancer, prolonged immobilization, and exogenous estrogen use.[32] Use of estrogen-containing oral contraceptive pills (OCPs) is associated with an increased risk of VTE among

premenopausal women (odds ratio [OR], 5.0; 95% confidence interval [CI], 4.2-5.8) compared to non-use.[33–35] Similarly, women who use estrogen-containing hormone replacement therapy (HRT) have a higher VTE risk (OR, 1.58; 95% CI, 1.52-1.64) than age-matched women who do not.[36] In both contexts, higher estrogen doses are associated with greater risk of VTE, and variability in risk magnitude is observed across different types of estrogens.[37] Progestin-only OCPs and hormone-releasing intrauterine devices (IUDs) do not appear to increase this risk, nor does transdermal preparation of HRT.[38] High levels of endogenous sex hormones are not associated with elevated VTE risk.[39] The risk of VTE in the setting of hormone therapy is not restricted to women or to cis gendered patients; testosterone therapy in men appears to be associated with increased VTE risk but is less well studied and the use of any exogenous hormones is pertinent history for any transgender or gender non-conforming patients.[40,41]

Sex-specific risk factors for PE are not well established outside of the peripartum period, and published data in this area are inconsistent. Several studies have found that men with PE are more likely to be smokers and to have concurrent chronic obstructive pulmonary disease[42–44]; this finding likely reflects a gendered behavior pattern in that men are more likely to smoke than women in the general population.[45] Men are also more likely than women to have active or recently treated cancer.[46–48] In contrast, women with PE are more likely to have recent immobilization, exogenous estrogen administration, and comorbid atrial fibrillation and congestive heart failure, although this association may reflect that women with PE are on average older than men.[44,47,49] Social determinants of health, such as patterns of exercise, diet, and access to health care also likely contribute to PE risk, but data are limited.

Sex differences are well documented in the incidence of recurrent VTE, although PE-specific data are more limited.[50–52] In fact, the largest study addressing this, which included over 55,000 patients, found that men had a 13% higher risk of VTE recurrence (95% CI, 1.07-1.19), which persisted at 5 years.[53] History of prior VTE is a stronger predictor of acute PE in men than in women, which is consistent with the higher rate of recurrence.[42]

2.2 | Clinical evaluation and diagnosis

Although there are sex-based differences in the presentation of acute PE, they are relatively minor. Patients of both sexes with acute PE most often present with dyspnea (56%–89% of patients), although women appear slightly more likely to report dyspnea than men. Chest pain is the second most common symptom among patients diagnosed with PE (14%–61%), which is slightly more common in men than women.[42,47,54,55] Syncope is less common as a presenting complaint (4%–22% of patients) and may be slightly more common in women, although a retrospective cohort study of over 300,000 patients concluded that the association between female sex and syncope was the result of confounding from demographic factors and medical comorbidities.[56] Hemoptysis is relatively uncommon as a presenting complaint (2%–7% of patients) but is slightly more common in men.[42,57] Calf pain also may be more predictive of PE in men than in women.[53]

The diagnostic approach to patients with suspected PE begins with assessment of pretest probability using clinical judgment and structured clinical decision tools. These tools, such as the Wells Score for PE and the revised Geneva Score, do not include sex as an objective risk factor.[58–61] The Wells score in particular was independently analyzed for any sex differences in performance and was found to perform equally well in women and men.[62] Patients with low pretest probability who meet all 8 Pulmonary Embolism Rule-out Criteria (PERC) may have PE excluded based on clinical grounds alone, whereas patients who do not meet PERC criteria or who have intermediate pretest probability require serum D-dimer testing. Individuals with abnormally elevated D-dimer levels or high pretest probability should receive diagnostic imaging to assess for PE.[63–66] Of note, both the PERC derivation and validation cohorts were approximately two-thirds women. Sex was evaluated in the derivation study but was not found to be significant and therefore is not included in the decision tool.[67] The 2008 validation study confirmed the performance of the sex-neutral tool in this population.[65] Structured clinical decision tools for assessing pretest probability of PE have equal efficiency and failure rates in women and men, though they likely have less specificity in women.[54,62]

Despite this structured approach to diagnostic evaluation and the similar overall incident rates of PE between men and women, major differences exist in the use and outcome of PE testing by sex. Women represent >60% of patients enrolled in many large studies of patients with suspected PE, suggesting that physicians may consider the diagnosis of PE more often in women.[68–71] Noninvasive testing has a greater yield in men, and women who are ultimately tested for PE using CTPA are 35%–55% less likely to be diagnosed with PE compared to similarly aged men.[54,62,72] Older data are consistent and found that women were more likely to undergo ventilation/perfusion scanning for PE as well.[73] Several potential mechanisms could contribute to this disparity, including a higher perceived risk of PE in women, sex-based differences in D-dimer test characteristics, or differences in the use or diagnostic performance of imaging tests, which are all areas of future investigation.

Differences in D-dimer levels may be partially responsible for the sex-based disparity in testing for acute PE. A greater proportion of men with suspected PE have the condition excluded based on D-dimer compared to women (43% vs 36%, $P = 0.001$).[54] Several factors likely contribute to this difference. Female sex has been associated with higher D-dimer values in several retrospective studies, and women who use exogenous estrogen have higher D-dimer levels than women who do not.[48,62,74–77] Furthermore, women with suspected PE are older on average compared to men, and age correlates positively with D-dimer levels.[13,47,78] There now exists a large body of literature that suggests the use of age-adjusted D-dimer cutoffs to improve the test's performance characteristics in patients over 50.[68,70,78] Although sex-specific D-dimer thresholds are not commonly used in clinical practice, such thresholds could increase the specificity of D-dimer testing in women. Sex-specific thresholds for other laboratory

values have been well studied, though they may be of unclear clinical significance. For example, a lower threshold for troponin has been proposed to identify myocardial injury and infarction in women, as women have smaller myocardial mass than men even when controlled for weight.[79,80] The first high-sensitivity cardiac troponin assay in the United States received approval with both combined and sex-specific thresholds;[81–83] similar thresholds are not approved for D-dimer assays.

There are relatively few studies on sex-related differences in imaging for PE. CTPA is the preferred imaging modality in both men and women.[84] In a subanalysis of the Prospective Investigation of Pulmonary Embolism Diagnosis II (PIOPED II) trial, CTPA had similar sensitivity and higher specificity (97% vs 93%, $P = 0.015$) for diagnosis of PE in in women compared to men, although the trial primarily used 4-slice computed tomography (CT) scanners that are not comparable to contemporary multislice CT systems.[85] Another small study found patient sex to have no effect on pulmonary blood flow during CTPA.[86] To our knowledge, there are no published data on the sex-specific performance of other diagnostic imaging modalities, including ventilation/perfusion scanning, and traditional pulmonary angiography.

2.3 | Severity assessment and treatment

Following diagnosis, assessment of PE severity is essential for guiding treatment and predicting outcomes, as severity can vary widely from mild symptoms to sudden death.[58,87,88] Clinical factors such as hypotension have greater value for predicting mortality than radiographic findings such as PE size or location.[89,90] High-risk PE (also classified as massive PE) is defined by hemodynamic instability and hypotension caused by acute right ventricular (RV) failure, and it carries a nearly 25% risk of mortality within 30 days.[91]

Hemodynamically stable patients with PE should be assessed using the well-validated PE Severity Index (PESI) or the simplified PESI (sPESI) to stratify patients into low, intermediate, and high risk categories with regard to 30-day mortality.[58] Individuals with low-risk scores (PESI class 1–2 or sPESI score of 0) have low 30-day mortality, and current guidelines do not universally recommend routine evaluation of RV function.[92,93] Patients with an intermediate-risk score (PESI class >2 or sPESI score >0) should be assessed for right heart strain via laboratory testing (elevated troponin or B-type natriuretic peptide [BNP]) and imaging (right ventricular strain on echocardiography or CT).[58] In the 2019 European Society for Cardiology (ESC) guidelines, patients with both laboratory and radiographic evidence of RV dysfunction are further classified as intermediate-high risk, whereas those with 1 or 0 indicators of RV dysfunction are classified as intermediate-low risk.[58]

Risk stratification tools may perform differently in men and women; however, tachycardia and hypoxia reliably predict adverse outcomes in both sexes.[57] Although sex was included in the 2005 PESI score, in the derivation of the simplified PESI score in 2010, it was not found to be a significant predictor of mortality.[91,94] The sPESI score has since been both internally and externally validated in cohorts that were predominantly female (55%-60%).[94,95] Although sex is not a factor in the sPESI, several studies have suggested that it may predict adverse outcomes more accurately in women than men despite that it performs well in both sexes.[57,96] In addition, using sex-specific biomarker cutoff values was shown to improve the performance and predictive value of the 2014 ESC guidelines, though this finding has not been replicated.[57] Future investigations should focus on sex-specific prognostic factors in acute PE.

Women are more likely than men to have severe clinical features of PE during admission, as evidenced by higher rates of hypotension and shock, higher pulmonary artery pressures, higher levels of BNP, and more frequent evidence of RV dysfunction on echocardiography.[44,47,50,55,97] There are minimal data available on sex differences in ECG. At least 1 study found that women may be more likely to have septal T-wave inversion, representing RV strain, although current guidelines do not include this criterion as a component of PE severity assessment.[48] In a prospective study over 10 years, Keller et al identified that women with PE were more likely to have evidence of RV dysfunction on echocardiography compared to men, although rates of RV dilation on CTPA were not significantly different.[57] Another study that included over 47,000 patients found a significantly higher percentage of women to have RV dysfunction on echocardiogram, as measured by tricuspid annular excursion and estimated pulmonary arterial pressures.[44] Unfortunately, neither study linked these findings with presenting chief complaint, though this does suggest that women may be more likely to experience dyspnea. Interestingly, a small prospective cohort found that women and men may have different patterns and rates of improvement of RV function as measured on echocardiogram.[98] Sex-specific patterns of RV strain and recovery are areas of interest for future research.

2.4 | Treatment and outcomes of high-risk PE

High-risk PE should be treated with systemic anticoagulation plus thrombolytic therapy unless absolutely contraindicated.[58,59,87,99] Patients with absolute contraindications or those who have refractory shock despite systemic thrombolysis may be considered for percutaneous catheter-directed treatment, surgical pulmonary embolectomy, or extracorporeal membrane oxygenation (ECMO).[58]

Despite data suggesting that women are more likely to present with high-risk features, several registry studies in the United States, Spain, and Japan suggest that rates of thrombolysis do not differ by sex, although conflicting data exist.[47,55,100] A prospective observational trial in Germany concluded that women were more likely to be treated with thrombolysis than men (16.4% vs 9.2%, $P = 0.013$),[101] whereas a retrospective cohort found the opposite, that women were significantly less likely to receive thrombolysis.[50] More research is needed to understand the effect of sex on guideline compliance and the decision to use or withhold thrombolysis in high-risk PE.[99,101]

Limited data exist regarding sex differences in use or outcomes of other reperfusion interventions. In a large study of over 300,000 patients with acute PE from the National Inpatient Survey, men were

statistically more likely to receive a surgical thrombectomy than women (3.0% vs 2.6%, $P = 0.007$), suggesting that women may be less likely to receive invasive interventions even when controlled for severity of illness.[46] ECMO is used only rarely in the treatment of acute PE and there is no published evidence regarding sex-specific use. In a retrospective study of 219 high-risk patients who were treated with ECMO, the majority of patients were male (67%) and female sex was found to be an independent predictor of mortality (OR, 2.19; 95% CI, 1.03-4.67), suggesting that women may be less likely to receive ECMO and women who do may have higher mortality.[102]

2.5 | Treatment and outcomes of intermediate- and low-risk PE

The mainstay of treatment for patients with low- and intermediate-risk PE is systemic anticoagulation; additional interventions can be considered for patients who have subsequent clinical deterioration. For these patients, treatment usually consists of systemic anticoagulation with heparins (unfractionated or low molecular weight), vitamin K antagonists (VKA), or direct oral anticoagulant (DOAC) medications.

DOACs have rapidly become the most common oral anticoagulant therapy for PE, replacing VKA in most situations, given their clinical efficacy and relative ease of administration.[103] The benefits of DOACs appear to be similar for men and women; there are no sex differences in the rates of recurrent VTE for patients on DOAC treatment.[104,105] Preliminary data from a large PE registry found that women with acute PE may be overall less likely than men to receive a DOAC (7.3% vs 8.0%, $P < 0.01$).[43]

Although anticoagulation is effective in treating PE and reducing recurrence in both men and women, women receiving anticoagulation therapy are more likely to experience bleeding complications and require blood transfusion.[43,44,47,55,100,103,105] This finding has been confirmed across many studies, both in PE and other cardiovascular disease states, and is likely multifactorial.[106,107] Although it is not addressed in all studies, menstrual bleeding may be an important contributor to clinically significant non-major bleeding in women only. Women treated with low molecular weight heparin (LMWH) receive higher average doses (IU/kg/day) compared to men.[43,44] Even when controlled for dose, women have higher serum levels of heparin and activated partial thromboplastin time levels,[108] suggesting a sex-influenced physiologic response. Among individuals with PE who are treated with VKA therapy, women are more likely to have supratherapeutic international normalized ratio levels (>3.0).[44] In those treated with DOACs, rates of major bleeding and clinically relevant non-major bleeding are 21% to 46% lower in men than in women as well.[103,105] Although some of these differences may be due to dosing, sex-based differences in absorption, distribution, pharmacokinetics, and excretion of anticoagulants may contribute to the increased rates of bleeding complications found in women. Alternatively, epidemiologic factors such as age and comorbidities may be to blame for the increased tendency of women to bleed, as suggested by a large database study that found sex alone not to be a risk factor for bleeding in a multivariate analysis.[44]

Patients who have absolute contraindications to anticoagulation, especially those with intermediate-high risk PE, may be considered for placement of an inferior vena cava (IVC filter). However, multiple studies have shown that women are also significantly less likely to receive IVC filters compared to men.[55,100]

Thrombolytics are not currently recommended for intermediate-risk patients, but studies have examined the risks and benefits of thrombolysis in this setting. Several of these suggest women may again have greater risks than men as noted for other PE treatments. In the Management Strategy and Prognosis of Pulmonary Embolism Registry (MAPPET), thrombolysis was associated with a statistically significant reduction in 30-day mortality for men (11.0% vs 2.7%; $P = 0.03$) but not women (11.1% vs 6.3%, $P = 0.18$).[109] Similarly, the Pulmonary Embolism-3 Trial found that women with intermediate-risk PE randomized to thrombolysis had a significantly higher rate of the primary outcome (a composite endpoint of in-hospital mortality or escalation of therapy) compared to men (relative risk 2.68 [1.34–5.36], $P = 0.005$).[89] Bleeding risks from thrombolysis were also shown to be greater in women, as 3 trials concluded that thrombolysis was associated with significantly higher rates of major bleeding (compared to placebo) in women but not in men.[89,101,109]

2.6 | Long-term outcomes

Despite the compelling data that women tend to present more often with high-risk PE, there is no clear evidence that their associated mortality is higher. Multiple studies, in fact, have found that men have higher PE-related and all-cause mortality than women.[42,110,111] Other studies have found no significant sex differences in PE-related mortality both short and long term.[46,57,112] Several studies have found that women had higher PE-associated mortality, though in some analyses controlled for severity this difference disappears.[47,55,100] Most studies of PE-related mortality are retrospective and have varying methodologies and primary outcomes, making it challenging to compare controlled analyses. Further characterization of any disparities in mortality by sex is another future research priority.

Differences in outcomes after PE extend beyond mortality. In a prospective multicenter observational study of patients with first-time PE, Kahn and colleagues demonstrated that women had lower quality of life, greater dyspnea, and lower exercise tolerance compared to men during 1 year of follow-up, even after adjusting for demographic factors, comorbidities, and PE severity.[113]

Sex- and gender-based differences are recognized in the prevalence, severity, treatment response, and survival of patients with certain types of pulmonary hypertension (PH). Pulmonary arterial hypertension (PAH), also described as Group 1 PH by the 2013 World Health Organization classification, occurs at higher rates in women than men, and women are more likely to develop PAH associated with connective tissue disorders such as systemic lupus erythematosus and systemic sclerosis.[114–116] Despite this higher incidence, women have

1- and 5-year mortality rates for PAH that are 10%–29% lower than in men.[117–119]

Sex differences are less well characterized in chronic thromboembolic pulmonary hypertension (CTEPH), classified as Group 4 PH, which has 75% lower prevalence than PAH.[119] Data are conflicting on whether CTEPH incidence varies by sex;[120–122] prospective longitudinal data from patients with first-time PE suggest that a univariate association between female sex and increased CTEPH incidence may be explained by confounders, such as PE severity and underlying hypercoagulable disorders.[121] Registry data suggest women with CTEPH have similar short-term mortality (ie, 1-year mortality) as men but significantly lower mortality rates beyond that time.[122] The role of sex hormones in CTEPH prognosis has not been described and is a research priority.

3 | CONCLUSION

Despite slight epidemiologic differences in risk across the lifespan, acute PE affects approximately equal numbers of women and men. Women are tested for PE at higher rates than men and an invasive workup is required more often in female patients. Among patients with confirmed PE, women tend to have more severe features yet may be less likely to receive invasive interventions. The reasons for these disparities are likely multifactorial but should be a research priority in order to provide equitable and evidence-based care for all of our patients.

AUTHOR CONTRIBUTIONS

AFJ and BCM conceived and outlined the manuscript. BEM, AFJ, and BCM developed the initial draft, including sections drafted by KSS and CDN. The manuscript was edited and completed by BEM, AFJ, and BCM. All authors made significant contributions to the manuscript and have reviewed and approved the final submission.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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