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SEX AS A VARIABLE IN HUMAN RESEARCH: A SYSTEMS APPROACH

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Reporting of sex as a variable in cardiovascular studies using cultured cells: A systematic review

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Abstract

Reporting the sex of biological material is critical for transparency and reproducibility in science. This study examined the reporting of the sex of cells used in cardiovascular studies. Articles from 16 cardiovascular journals that publish peer-reviewed studies in cardiovascular physiology and pharmacology in the year 2018 were systematically reviewed using terms "cultured" and "cells." Data were collected on the sex of cells, the species from which the cells were isolated, and the type of cells, and summarized as a systematic review. Sex was reported in 88 (38.6%) of the 228 studies meeting inclusion criteria. Reporting rates varied with *Circulation, Cardiovascular Research* and *American Journal of Physiology: Heart and Circulatory Physiology* having the highest rates of sex reporting (>50%). A majority of the studies used cells from male (54.5%) or both male and female animals (32.9%). Humans (31.8%), rats (20.4%), and mice (43.8%) were the most common sources for cells. Cardiac myocytes were the most commonly used cell type (37.0%). Overall reporting of sex of experimental material remains below 50% and is inconsistent among journals. Sex chromosomes in cells have the potential to affect protein expression and molecular signaling pathways and should be consistently reported.

KEYWORDS

cardiology, cells, culture, endothelium, myocyte, sex, vascular smooth muscle

1 | INTRODUCTION

Sex chromosomes are present in all nucleated mammalian cells and have the potential to influence the expression of proteins, receptors, and other signaling molecules.[1-15] Cultured cells are used to identify molecular signaling pathways that inform the physiology, pathophysiology, disease progression, and potential treatment targets in vitro.[13] Sex differences in gene expression, proliferation, migration, and response to activation have been identified in vascular smooth muscle cells, endothelial cells, and cardiac myocytes.[4,16-22]

Therefore, sex is an essential biological variable in pre-clinical and clinical studies.[8,10] Despite a 2001 Institute of Medicine report noting the importance of sex as a biological variable in preclinical and clinical studies, previous work from 2011 noted that only 28% of top cardiovascular journals reported the sex of cultured cells.[13] The absence of this variable in reporting methods has crucial downstream influences on the development of therapeutic targets in cardiovascular disease. In addition to the obvious differences in reproductive structure and function, sex influences all physiological systems to determine human physiology, pathophysiology of disease, and clinical response to therapies.[2-4,6]

Despite significant progress in health care delivery, cardiovascular disease remains a leading cause of mortality and morbidity worldwide.[23-68] Multiple prior clinical cardiovascular studies demonstrate sex-specific differences in the receipt of therapy, response to therapy, and clinical outcomes.[37,40,46,58,68] In addition, conditions such as heart failure with preserved ejection fraction, Takotsubo cardiomyopathy, and spontaneous coronary artery dissection demonstrate a strong female preponderance.[44,69,70] Demographic factors such as age, sex, race, socioeconomic status, and zip code influence access to health care, compliance with medications, response to therapy and clinical outcomes in the short- and long-term.[23,25,27,36,40,44,46,47,51-53,58,71-80] Therefore, in the translational science spectrum, it is crucial to report sex-specific data in experiments and clinical studies, since it has a direct correlation with disparities in outcomes. In 2014, the National Institutes of Health reemphasized the importance of sex as a biological variable for transparency and reproducibility of scientific data.[81] Therefore, in light of this policy, this study sought to systematically review the implementation of reporting of sex in cultured cells used in contemporary cardiovascular studies.

2 | MATERIALS AND METHODS

2.1 | Data sources and search strategies

To update a prior systematic review,[13] Ovid MEDLINE(R) was searched from 2018 to November 8, 2019. The search strategy was designed and conducted by an experienced librarian with input from the study's first and senior authors (SV, VMM). Cardiovascular journals with the top impact factors in ISI Web of Knowledge (2018) under the subject category "cardiac and cardiovascular systems" were searched with keywords for "cultured" and "cells" as detailed in the Supplemental material. Types of cells included myocytes, endothelial cells, vascular smooth muscle cells, cardiomyocytes (including neonatal cardiomyocytes), cardiac fibroblasts (including neonatal cardiac fibroblasts), stem cells, progenitor cells, and pluripotent stem cells. The top 10 cardiovascular journals were included, eliminating those that published only review articles. Journals selected in the descending order of impact factor included: *European Heart Journal, Circulation, Journal of the American College of Cardiology, Circulation Research, European Journal of Heart Failure, Journal of the American Medical Association Cardiology, Journal of the American College of Cardiology: Cardiovascular Imaging, Journal of the American College of Cardiology: Cardiovascular Interventions, Journal of the American College of Cardiology: Heart Failure,* and *Journal of Heart and Lung Transplant.* The journal *Arteriosclerosis, Thrombosis and Vascular Biology* was not listed under the subject category mentioned above; however, because of its high impact factor in the cardiovascular field, it was included. Additional high impact journals that published basic science articles in cardiovascular medicine were included: *Cardiovascular Research, Journal of Molecular and Cellular Cardiology, American Journal of Physiology: Heart and Circulatory Physiology, Journal of Cardiovascular Pharmacology,* and *Federation of American Societies for Experimental Biology (FASEB) Journal.* The year was limited to "2018" or to the issue(s) that corresponded to the year 2018. Results from these searches were then sorted by best match (relevance). Studies designed as case reports, systematic or narrative reviews, and studies without relevant outcomes were excluded. Consistent with prior study designs, abstracts presented at professional societal meetings were excluded since they are subject to a higher risk of bias due to the lack of rigorous peer review.[26,40,42,52,57]

The resultant abstracts were screened by two independent reviewers (SS, SPP). All references of included studies were evaluated for additional studies. Study inclusion was based on the consensus of the two reviewers. A third independent reviewer (PRS) in coordination with the first author (SV) served as the referee in case of disagreement between the first two reviewers. Data were collected on the sex of cells, scored as "yes" for sex reported and "no" for no sex reported. The "yes" was further categorized into males, females, or both. Additionally, the species from which the cells were isolated and the type of cells used were recorded. The available evidence was summarized as a systematic review.

3 | RESULTS

The search strategy identified 1311 abstracts in the year 2018 or to the issue(s) published in the year 2018 that met the inclusion criteria. Of these, 228 met the final inclusion criteria and were included in the qualitative analysis (Figure 1). No studies meeting our inclusion criteria were identified in *European Journal of Heart Failure, Journal of the American Medical Association Cardiology, Journal of the American College of Cardiology: Cardiovascular Imaging, Journal of the American College of Cardiology: Cardiovascular Interventions, Journal of the American College of Cardiology: Heart Failure, Journal of Heart and Lung Transplant,* and *Federation of American Societies for Experimental Biology Journal.* The sex of cells used for cultures was reported in 88 (38.6%) of the studies within the body of the article. Among the included journals, the number of studies per journal varied between 59 for *Journal of Molecular and Cellular Cardiology* and 3 for the *Journal of the American College of Cardiology* (Figure 2). Of the surveyed journals, *Circulation, Cardiovascular Research* and *American Journal of Physiology: Heart and Circulatory Physiology* had the highest rates of sex reporting (>50%) (Figure 2 and Table 1). In the studies that reported the sex of cells, a majority used male cells or both male and female cells combined, but no studies used exclusively female cells (Figure 2). In the 228 studies that were reviewed humans, rats and mice were the most commonly used sources of cells (Figure 3); cardiomyocytes, endothelial cells, and vascular smooth muscle cells were the most commonly used cell types (Figure 4).

4 | DISCUSSION

In this systematic review of high impact cardiovascular specialty journals, there remains a large inconsistency in the reporting of the sex of cells used in the basic studies of

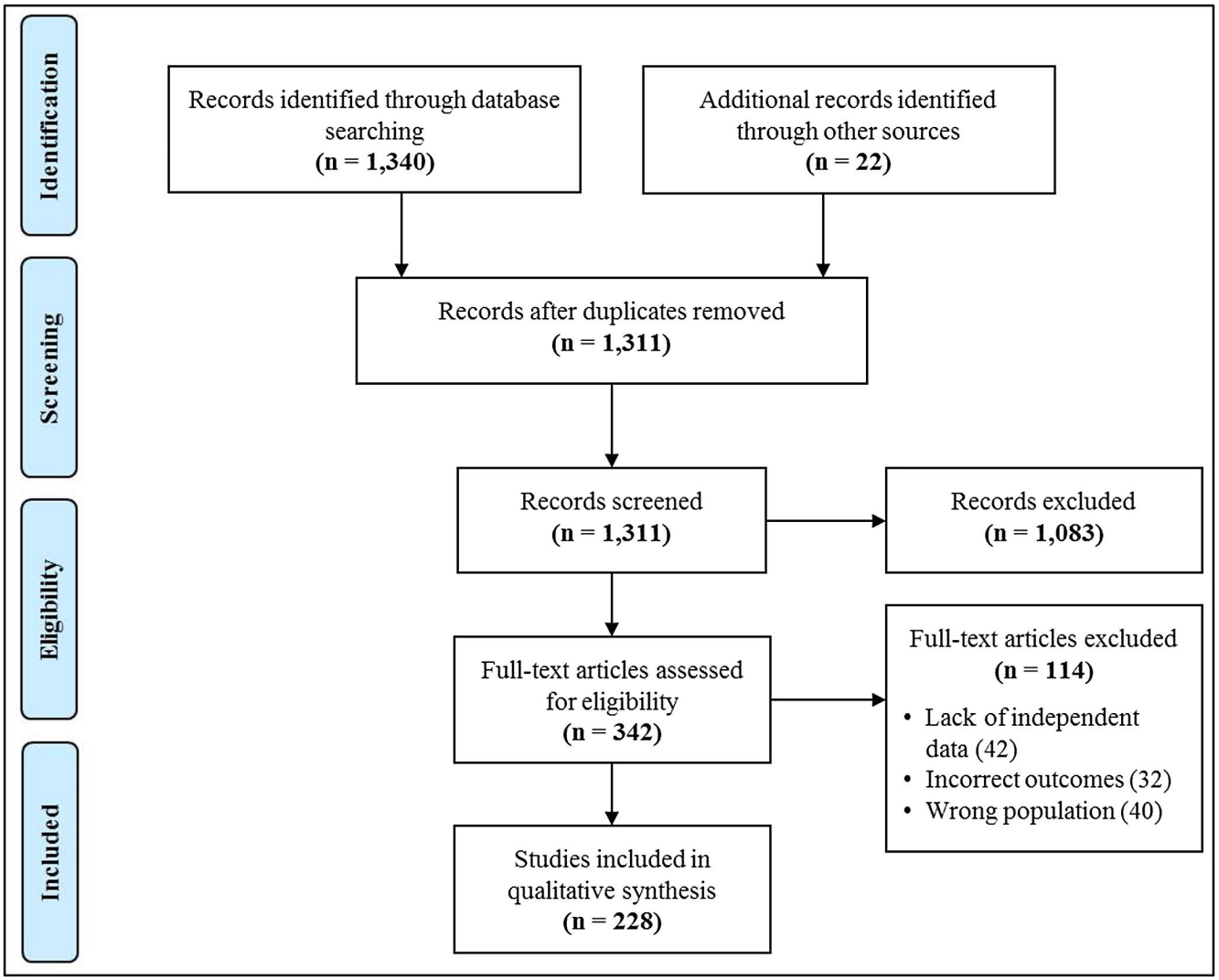

FIGURE 1 Literature search strategy

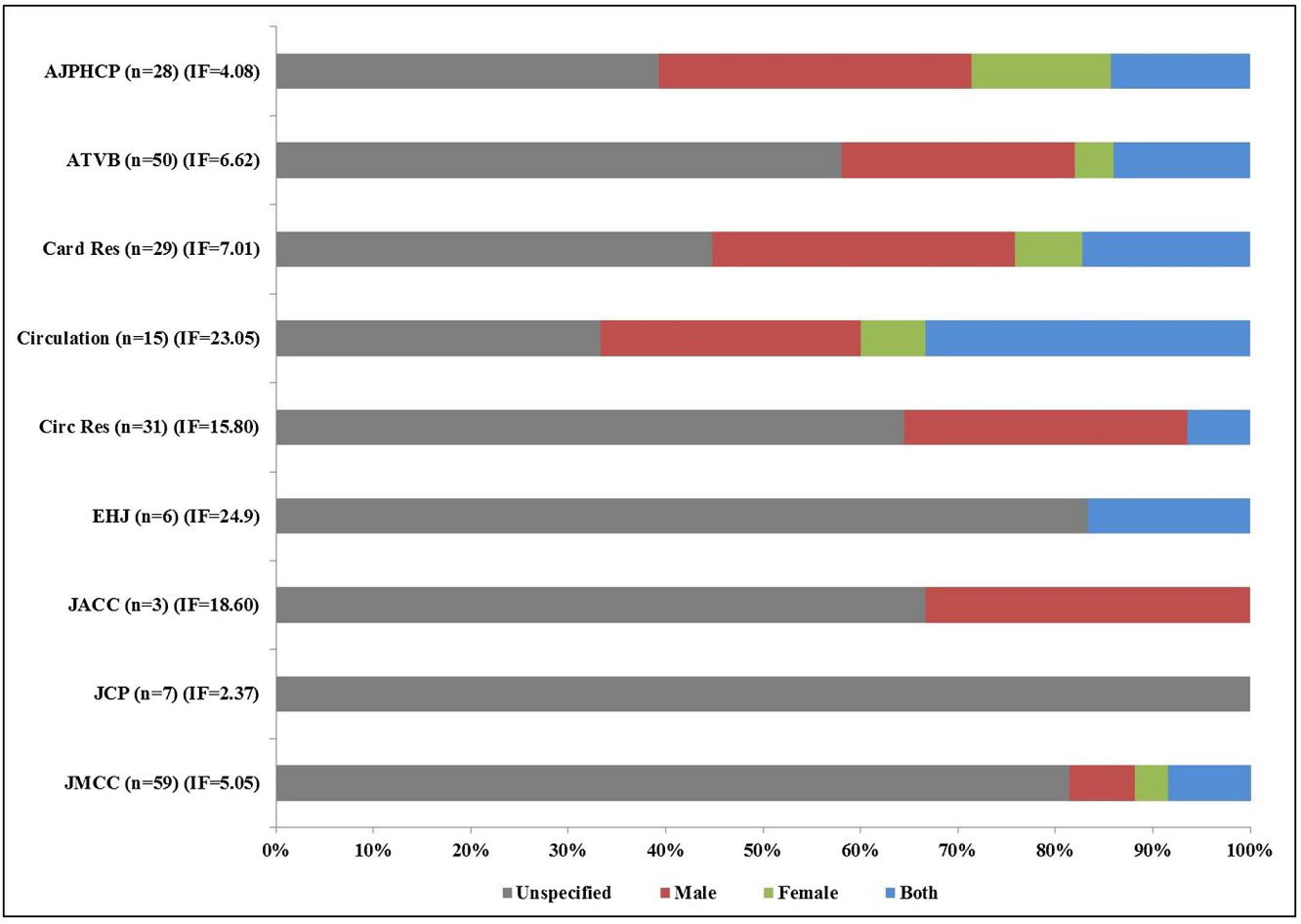

FIGURE 2 Percentages of articles meeting the inclusion criteria for in vitro experiments that reported the sex of cells published in key cardiovascular journals in 2018. AJPHCP: *American Journal of Physiology: Heart and Circulatory Physiology*; ATVB: *Arteriosclerosis, Thrombosis and Vascular Biology*; Card Res: *Cardiovascular Research*; Circ Res: *Circulation Research*; EHJ: *European Heart Journal*; JACC: *Journal of the American College of Cardiology*; JCP: *Journal of Cardiovascular Pharmacology*; JMCC: *Journal of Molecular and Cellular Cardiology;* IF*: impact factor*

cardiovascular-derived cells in spite of many regulatory mandates from funding agencies to include cells (and animals) of both sexes in research studies.[82] Although there is a near doubling in the reporting of sex of cells in studies of comparable journals from 19.8% in 2010[13] to 38.6% in 2018 (present study), only three of the 10 journals surveyed had reporting rates of >50% in 2018 (Figure 2 and Table 1). Thus, there remains a significant difference among journals on the reporting of this critical information that is needed for transparency and reproducibility/ validation of data. There also remains a lack of understanding on the part of researchers that sex is a biological variable paramount to the structure and regulation of intracellular mechanisms.[83] The belief that cellular pathways common to both male and female cells are regulated similarly needs to be reconsidered, that is, a common cellular pathway may be regulated differently in male and female cells. Even though studies included cells from both sexes, they were evaluated together, and therefore, sex-specific data were not reported.

The lack of due diligence on the part of journal reviewers and editors to monitor the reporting of the sex of cells continues. Of the 16 journals reviewed, 11 (68.8%) have editorial policies and guidelines regarding how the sex of experimental material is to be reported. The use of cultured cells in basic physiology and pharmacology is fundamental to understanding regulatory mechanisms that could identify potential targets for the development of new therapeutic approaches to disease. In the current preventative, diagnostic and therapeutic strategies, there is limited application of sex-specific definitions and normative ranges for clinical parameters both of which contribute to the absence of personalized care, specifically for women.[2,83] These issues are even more pervasive in basic science wherein sex is either not reported or research is restricted to male species to prevent the confounding effect of hormones of the strategy or therapy being evaluated.[11,84] Indeed as noted in this review, a majority of the studies did not report the sex of the cells, and the ones that did were usually reported as using male cells.

TABLE 1 Comparison of papers reporting of sex of cells used in cardiovascular studies in 2010 and 2018

Journal	Editorial policy on sex reporting	Journal articles in 2010 (N = 101)		Journal articles in 2018 (N = 228)	
		Total articles	Percentage reporting sex	Total articles	Percentage reporting sex
American Journal of Physiology: Heart and Circulatory Physiology	Yes	10	50	28	61
Arteriosclerosis, Thrombosis, and Vascular Biology	Yes	10	20	50	42
Cardiovascular Research	No	10	10	29	55
Circulation	Yes	20	15	15	67
Circulation Research	Yes	10	35	31	35
European Heart Journal	No	7	0	6	17
Journal of the American College of Cardiology	Yes	6	0	3	33
Journal of Cardiovascular Pharmacology	No	4	50	7	0
Journal of Molecular and Cellular Cardiology	No	20	15	59	19

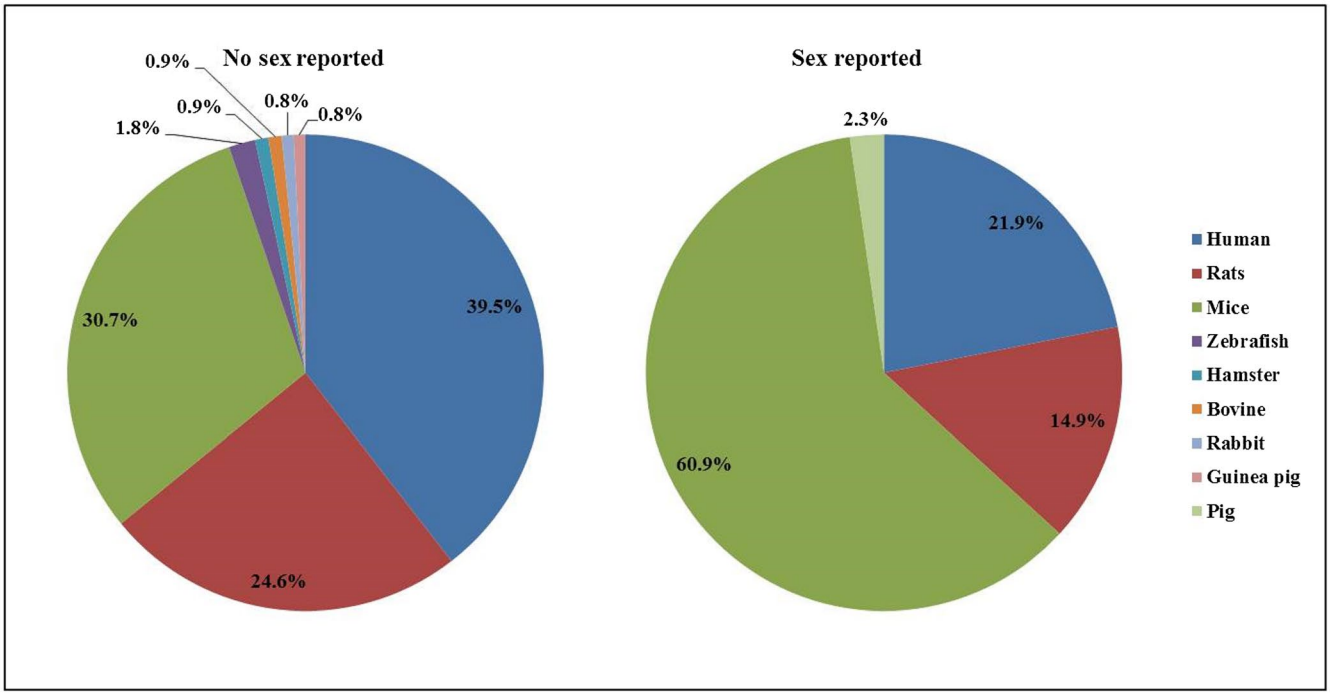

FIGURE 3 Sources of cultured cells in studies, which met inclusion criteria, stratified by sex reporting. Representation of species for sources of cells (by percentage) which (A) reported (n = 88 articles) and (B) did not report (n = 140) the sex of cells. Some studies used more than one species

For approximately 20 years beginning in 1993 with the National Institutes of Health Revitalization Act mandating the inclusion of women and minorities in clinical research, the 2001 Institute of Medicine report emphasizing the influence of sex on health and disease from "womb to tomb", and the 2014 mandate to include sex as a biological variable in grants funded by the National Institutes of Health in the United States, as well as other agencies globally, there remains a persistent gap in the inclusion and, reporting on female cells, tissues and animals. Therefore, to have sex and age-appropriate studies of female species remains an unfulfilled priority in basic and translational research.[2] To fulfill this priority requires the deliberate and diligent effort of individual scientists, journal reviewers, editors, and editorial policies.

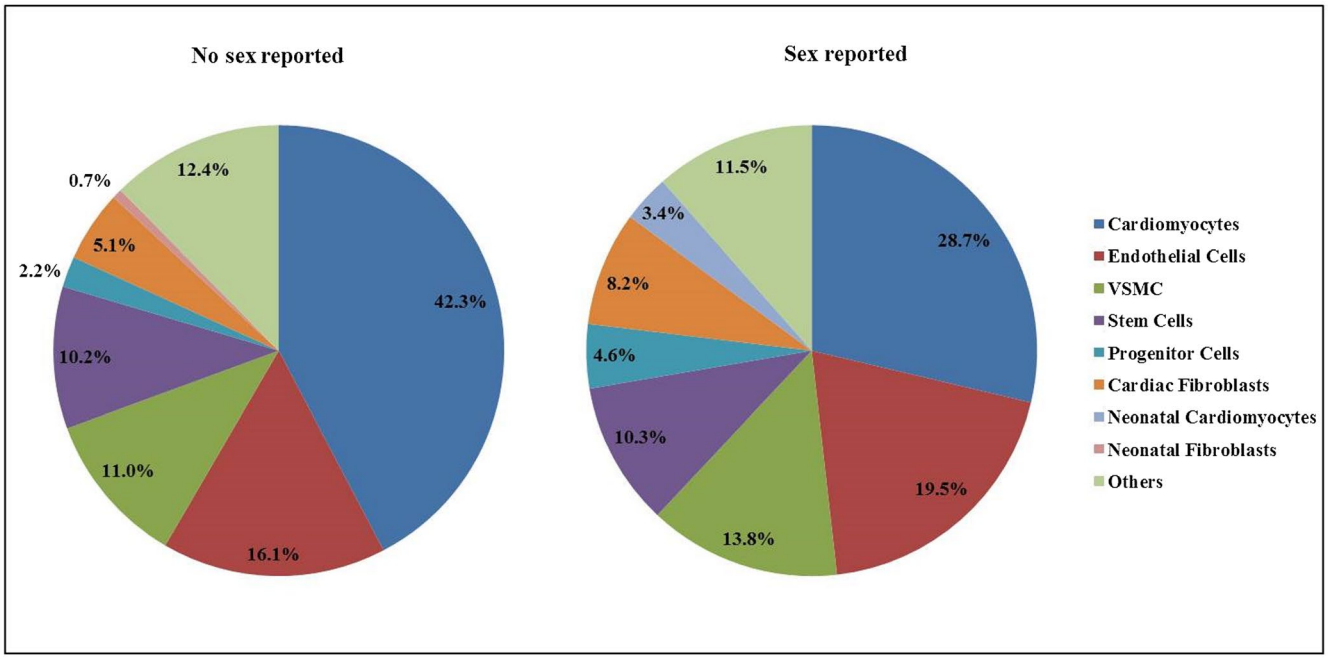

FIGURE 4 Types of cells used in studies, which met inclusion criteria, stratified by sex reporting. Representation of cell types (by percentage) which (A) reported (n = 88 articles) and (B) did not report (n = 140) the sex of cells. Some studies used more than one type of cell. Others: Platelets, megakaryocytes, hepatic cells, hepatocellular carcinoma cells, kidney cells, and adipocytes

4.1 | Limitations

There are several limitations to this systematic review. First, only studies published in 2018 were reviewed, and, therefore, it is not possible to comment on whether the increase in reporting is a linear or exponential trend. Second, despite editorial policies on the reporting of the sex of cells in studies published in these journals, information was not sought from journal editors/editorial boards on how these policies were implemented. Finally, we reviewed only papers reporting the use of cultured cells published in cardiovascular specialty journals, and, therefore, cannot comment on other sources of literature or other disciplines.

5 | CONCLUSIONS

This systematic review notes a nearly doubling in the reporting of the sex of cultured cells in cardiovascular high impact journals since 2010. Despite this encouraging trend, the wide variation in reporting practices among individual journals and the overall low reporting rate of the sex of cells (<40%) indicates that more rigorous and deliberate attention to sex as a biological variable is needed by authors and editors in pursuit of scientific excellence in the field of cardiovascular medicine.

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CONFLICT OF INTEREST

All authors do not report any financial or intellectual conflicts of interest with this submission.

AUTHOR CONTRIBUTIONS

Study design, literature review, data analysis, and statistical analysis: SV, SPP, SS, and PRS.

Data management, data analysis, and drafting manuscript: SV, SPP, SS, and PRS.

Access to data: SV, SPP, SS, PRS, and VMM.

Manuscript revision, intellectual revisions, and mentorship: SV and VMM.

Final approval: SV, SPP, SS, PRS, and VMM.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

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