

PRECLINICAL RESEARCH

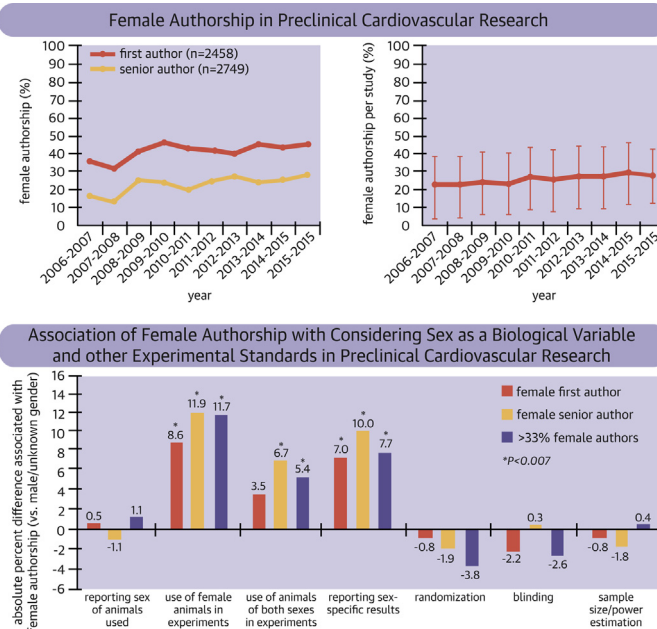
Female Authorship in Preclinical Cardiovascular Research

Temporal Trends and Influence on Experimental Design

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VISUAL ABSTRACT



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HIGHLIGHTS

- In this analysis of 3,396 preclinical studies published in 5 leading cardiovascular journals over a 10-year period, women accounted for 24 ± 17% of authors per manuscript.
- Female authorship is increasing in preclinical cardiovascular science, but the proportions of articles with first and senior authors of different sex have remained unchanged, which suggests that segregation by sex in mentorship relationships exists and persists.
- In preclinical studies that reported the sex of the animals used, female authorship was positively associated with studying female animals, using animals of both sexes, and reporting sex-specific results, which are findings that persisted in adjusted and sensitivity analyses.
- Author sex was not associated with other measures of methodological rigor or with 60-month citation counts.

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ABBREVIATIONS
AND ACRONYMS

CI = confidence interval

NIH = National Institutes of
Health

OR = odds ratio

SUMMARY

In this analysis of 3,396 preclinical cardiovascular studies, women were first, senior, and both first and senior authors in 41.3%, 20.7%, and 11.0% of the studies, respectively. Female authorship increased over a 10-year period. However, the proportion of studies with first and senior authors of differing sex was low and stable, suggesting that segregation by sex in mentorship relationships exists and persists. Female authors were more likely to consider sex as a biological variable, but author sex was not associated with other measures of experimental rigor or research impact, indicating that women's underrepresentation was not due to differences in research capacity or impact. (J Am Coll Cardiol Basic Trans Science 2019;4:471-7) © 2019 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

The now outdated axiom that cardiovascular disease is a disease of men began to be meaningfully challenged in the 1980s, with considerable effort focused on adequately representing women in clinical trials. Central to many of these initiatives was (and continues to be) the recognition that fundamental yet poorly understood differences exist between men and women, and that these differences could engender health disparities if ignored. However, this “revolution” has not permeated preclinical stages of research, which serve to inform clinical trials. The preferential use of male animals and a lack of sex-disaggregated reporting is increasing in cardiovascular science (1), despite the emphasis of the National Institutes of Health (NIH) on considering sex in preclinical research as important for advancing the health of women (2) and despite its feasibility in most research settings (3). This bias has the potential to undermine advances made in clinical trial design by skewing our understanding of disease processes and the effectiveness of potential therapies (4).

SEE PAGE 478

It has been argued that the participation of women in research enhances knowledge outcomes and scientific progress (5), in part via enhanced exploration of sex differences (6). If true, sex gaps in medicine and research—including the underrepresentation of women in fields such as cardiology (7) and the relative lack of adequate mentorship for women (8)—would not only have important societal implications but also meaningful scientific ramifications. Recognizing this possibility, the NIH has emphasized their commitment to diversity in the biomedical research workforce (including better representation of women) and

identified assessing the impact of this diversity on the quality and outputs of research as 1 of 4 major diversity challenges facing the biomedical “ecosystem” (9).

We therefore examined a large body of leading preclinical cardiovascular research to explore potential differences in experimental rigor between male and female researchers, focusing on the inclusion of female animals in experiments and on analyses of sex differences. Temporal trends in female authorship and patterns in mentorship relationships by sex were examined as secondary analyses. We hypothesized that female authorship and mentorship relationships between men and women had both increased, but that these would not be associated with increased consideration of sex as a biological variable or with other measures of experimental rigor.

METHODS

As described (10), all preclinical studies published between July 2006 and June 2016 in *Circulation*; *Circulation Research*; *Hypertension*; *Stroke*; and *Arteriosclerosis, Thrombosis, and Vascular Biology* were reviewed. Studies were included if they reported original data from in vivo experiments using nonhuman mammals and proposed therapeutic applications or implications to specific human disorders. Pre-specified variables collected included the disease studied, the animal model(s) used and their sex, and whether any study result was reported by sex. Because of the possibility that differences in female animal inclusion or sex-specific analyses might be attributable to broader differences in experimental design, we also analyzed whether animals were randomized, whether blinding was used (concealed allocation or

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blinded outcome assessment), and whether sample size and/or power estimations were performed.

Study author names were extracted from Scopus. Author sex was determined using the online database genderize.io, which included >216,000 first names across 79 countries and 89 languages when queried. The database determines the sex of a name with an associated certainty factor. First authors are generally considered to have executed most of the published work, whereas senior authors are usually the study supervisors or principal investigators, and are generally considered to have contributed most to study planning and design (11,12); therefore, these were selected as our primary analyses. Female authorship as a proportion of all authors per manuscript was examined as a secondary analysis (per 10% increase and dichotomized as $\geq 33\%$ of authors). Scopus was also queried to determine citation counts at 60 months for articles published between July 2006 and June 2011, as described (10). Post hoc analyses of mentorship relationships by sex were performed, with senior authors designated as mentors and first authors as mentees. A certainty factor of $\geq 70\%$ was used to assign author sex for all analyses, otherwise sex was considered unknown. Articles with authors of unknown sex were excluded in primary analyses but were included in secondary and post hoc analyses to minimize missing data. Sensitivity analyses using a certainty factor of $\geq 90\%$ for author sex and of sex-specific reporting restricted to studies in which animals of both sexes were used were performed.

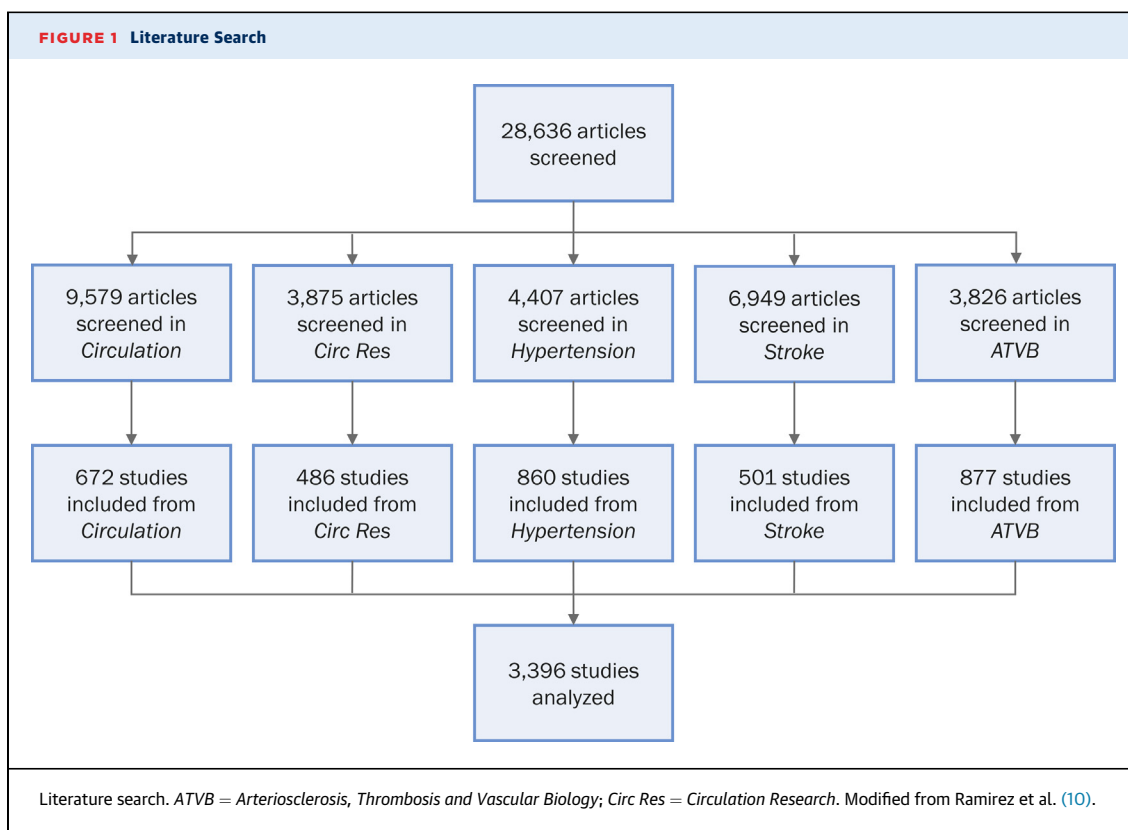
Categorical variables are reported as number (percentage) and were compared using chi-square tests. Continuous variables are reported as mean $\pm$ SD or median with interquartile range (25th to 75th percentiles) (IQR) and were compared using Student's *t*-tests or Mann-Whitney U tests, respectively. Temporal trends were assessed using Cochran-Armitage tests or Spearman's rank-order correlation (ρ) using 12-month intervals. The associations of author sex with factoring sex of the animals studied in the reporting, design, and analysis of experiments and with the implementation of other study design elements were examined using chi-square tests (reported as absolute percent differences in study characteristics) and via simple and multivariable logistic regression (reported as odds ratios [ORs] with 95% confidence intervals [CIs]). Citation count comparisons were performed via stratification and multivariable linear regression. All analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina) using a 2-tailed α level of 0.05 (corrected using the Bonferroni method to account for multiple comparisons when specified).

RESULTS

Of 28,636 articles screened, 3,396 met the study inclusion criteria (Figure 1). Women accounted for $24 \pm 17\%$ of authors per manuscript, with 542 articles (16.0%) not including any female authors and none being authored solely by women. After excluding articles with authors of unknown sex, women were identified as first authors of 1,016 of 2,458 articles, senior authors of 569 of 2,749 articles, and both first and senior authors of 235 of 2,135 preclinical studies (41.3%, 20.7%, and 11.0%, respectively). The distribution of observed mentorship relationships differed from the expected distribution, with disproportionately high numbers of same-sex mentorships identified ($p < 0.001$), including a relative 50% greater than expected frequency of male to male mentorships. No difference was observed in the number of coauthors of articles with female versus male first or senior authors (9.6 vs. 9.6; $p = 0.864$; and 9.2 vs. 9.5; $p = 0.075$; respectively). Five-year citation counts were comparable between female and male authors (21 [interquartile range (IQR): 13 to 31] vs. 20 [IQR: 12 to 33]; $p = 0.509$ for first authors; 18 [IQR: 12 to 30] vs. 20 [IQR: 13 to 31]; $p = 0.170$ for senior authors). Author sex was similarly not predictive of citation counts in multivariable models that adjusted for cardiovascular disease studied, publication date, and journal.

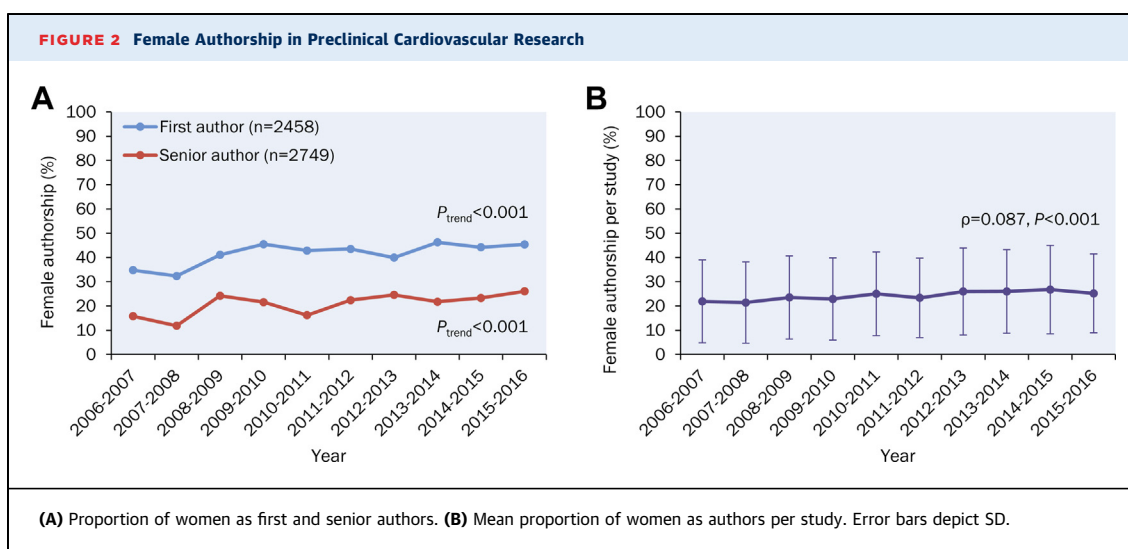
Temporal analyses over 10 years indicate that the proportions of female first and senior authors each increased, with women accounting for between 32.3% and 46.3% of first authors and between 11.8% and 26.1% of senior authors (Figure 2A). There was a corresponding temporal increase in the proportion of manuscripts with women as both first and senior authors (full range: 5.5% to 14.9%; $p_{\text{trend}} = 0.001$). The proportions of articles with first and senior authors of differing sex did not change (full range: 28.5% to 34.3%; $p_{\text{trend}} = 0.663$ for female first and male senior authorship; full range: 5.5% to 14.9%; $p_{\text{trend}} = 0.184$ for male first and female senior authorship). Per article, the mean proportion of female authors slightly increased (full range: 21.4% to 26.8%; $p < 0.001$) (Figure 2B).

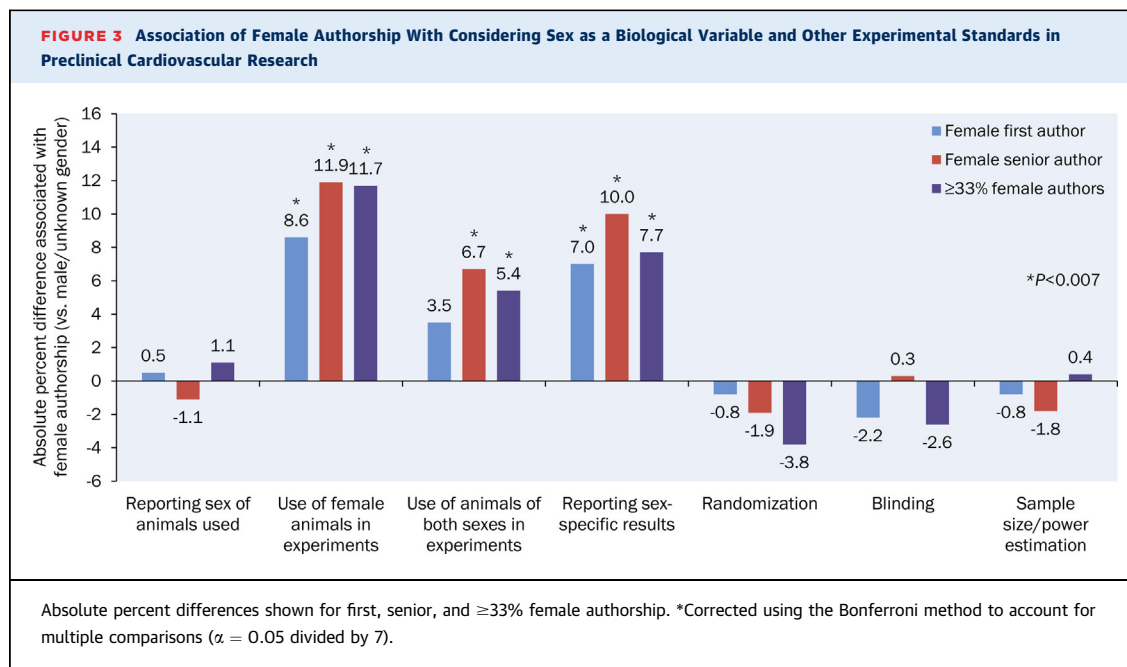
Female and male authors were equally likely to report the sex of animals used in preclinical experiments (815 of 1,016 [80.2%] vs. 1,150 of 1,442 [79.8%]; $p = 0.776$ for first authors; 455 of 569 [80.0%] vs. 1,767 of 2,180 [81.1%]; $p = 0.556$ for senior authors). However, when the sex of the animals was reported, women were more likely to have used female animals in their experiments (292 of 815 [35.8%] vs. 313 of 1,150 [27.2%], $p < 0.001$ for first authors; 181 of 455 [39.8%] vs. 492 of 1,767 [27.8%]; $p < 0.001$ for senior



authors), to have used animals of both sexes (156 of 815 [19.1%] vs. 179 of 1,150 [15.6%]; $p = 0.038$ for first authors; 98 of 455 [21.5%] vs. 262 of 1,767 [14.8%]; $p < 0.001$ for senior authors), and to have reported sex-specific results (326 of 815 [40.0%] vs. 380 of 1,150 [33.0%]; $p = 0.002$ for first authors; 199 of 455

[43.7%] vs. 597 of 1,767 [33.8%]; $p < 0.001$ for senior authors). Similar findings were observed when female authorship was examined as a proportion of all authors per manuscript. In contrast, female authorship was not associated with randomization, blinding, or sample size estimation after correcting for multiple





comparisons (Figure 3). The preceding differences persisted when female authorship was examined on an interval scale (per 10% increase) and after adjusting for pre-specified potential confounders (Table 1). All findings were also comparable in sensitivity analyses using a minimum certainty factor of 90% for author sex. When restricted to studies that included both male and female animals ($N = 335$ to 421), female senior authorship (but not first or cumulative authorship) remained associated with reporting sex-specific results after adjusting for pre-specified potential confounders (OR: 2.2; 95% CI: 1.1 to 4.4; $p = 0.036$).

DISCUSSION

Sex differences in innate scientific ability have long ago been refuted (13); however, career trajectories and personal and professional experiences often differ between male and female academics (8,13), which may influence researchers' priorities and practices. Although there are clear societal benefits to promoting sex inclusivity in research, its impact on the quality and impact of research remains unexplored (9). Our analysis of preclinical cardiovascular research demonstrates that: 1) approximately 41% of first authors and 21% of senior authors over a recent 10-year period were women; 2) although female authorship is increasing, segregation by sex in mentorship relationships exists and persists; and 3) when women influence experimental design and

reporting or are a larger proportion of the research team, studies are more likely to include female animals and to explore sex-based differences, but author sex is not associated with other measures of methodological rigor or research impact.

Preclinical research using animal models often precedes and informs clinical trials. However, important and remediable methodological shortcomings remain prevalent in preclinical cardiovascular research (10), including a tendency to exclude females in animal experiments and to ignore the potential influence of sex on study outcomes (1). Women's perspectives have been suggested to uniquely promote scientific progress in general and advances in women's health in particular, in part due to their greater tendency to explore the effects of gender and sex (5,6). Our data suggest that women are indeed more attuned to considering sex as a biological variable in preclinical experiments, but that male and female researchers are more alike than they are different when broader measures of scientific rigor and research impact are considered.

A corollary to the previously described findings is that the persistent underrepresentation of women in preclinical cardiovascular research is highly unlikely to be attributable to differences in research capacity or potential impact. Rather, systemic factors are probably influential. For instance, although modern scientific endeavors are increasingly reliant on research teams and networks—settings in which a diversity of viewpoints and experiences are sought

TABLE 1 Association Between Female Authorship and Experimental Design Characteristics in Preclinical Cardiovascular Studies

	N*	Crude OR (95% CI)	Adjusted OR (95% CI)†	p Value‡
Female first author				
Reporting sex of animals	2,458	1.03 (0.84–1.26)	0.96 (0.77–1.19)	0.698
Inclusion of female animals‡	1,965	1.49 (1.23–1.81)	1.60 (1.30–1.96)	<0.001
Inclusion of animals of both sexes‡	1,965	1.28 (1.01–1.63)	1.29 (1.01–1.66)	0.046
Sex-specific reporting of results‡	1,965	1.35 (1.12–1.63)	1.33 (1.10–1.62)	0.004
Randomization	2,458	0.95 (0.78–1.16)	1.03 (0.83–1.28)	0.776
Blinding	2,458	0.91 (0.76–1.08)	0.95 (0.79–1.15)	0.608
Sample size estimation	2,458	0.70 (0.41–1.20)	NR	
Female senior author				
Reporting sex of animals	2,749	0.93 (0.74–1.18)	0.83 (0.65–1.07)	0.153
Inclusion of female animals‡	2,222	1.71 (1.38–2.12)	1.81 (1.43–2.28)	<0.001
Inclusion of animals of both sexes‡	2,222	1.58 (1.22–2.04)	1.58 (1.20–2.08)	0.001
Sex-specific reporting of results‡	2,222	1.52 (1.24–1.88)	1.44 (1.16–1.79)	0.001
Randomization	2,749	0.90 (0.71–1.12)	0.88 (0.68–1.13)	0.308
Blinding	2,749	1.02 (0.84–1.23)	1.14 (0.92–1.42)	0.219
Sample size estimation	2,749	0.32 (0.13–0.80)	NR	
Female authorship (per 10% increase)				
Reporting sex of animals	3,396	1.04 (0.98–1.09)	1.02 (0.97–1.09)	0.435
Inclusion of female animals‡	2,718	1.20 (1.14–1.26)	1.20 (1.13–1.26)	<0.001
Inclusion of animals of both sexes‡	2,718	1.13 (1.07–1.21)	1.12 (1.05–1.20)	<0.001
Sex-specific reporting of results‡	2,718	1.13 (1.08–1.19)	1.11 (1.05–1.17)	<0.001
Randomization	3,396	0.95 (0.90–1.00)	1.00 (0.94–1.06)	0.949
Blinding	3,396	0.99 (0.94–1.03)	1.04 (0.99–1.09)	0.173
Sample size estimation	3,396	1.08 (0.94–1.24)	NR	

*Refers to the total number of studies included in analyses. †Adjusted for disease studied, animal model(s) used, journal of publication, date of publication, and number of co-authors. ‡Analysis restricted to studies in which the sex of animals used was reported. Bonferroni corrected α level of 0.007 used to define statistical significance ($\alpha = 0.05$ divided by 7).

CI = confidence interval; NR = not reported due to small number of events per predictor variable; OR = odds ratio.

and valued (6)—our analysis highlights a persistent predominance of same-sex mentorships. Because of the relative paucity of available female mentors, this practice has the potential to perpetuate women's underrepresentation in the field and to hinder efforts to improve the status quo (7).

STUDY LIMITATIONS. The journals examined were selected based on their prominence in cardiovascular research, their collective focus on a wide range of cardiovascular disorders, and their endorsement of NIH guidelines on rigor and reproducibility (10). However, they might not be representative of all preclinical cardiovascular journals. Author sex was determined using an arbitrary certainty factor, which might have resulted in misclassification in a minority of cases. However, our results were comparable in sensitivity analyses using a more stringent criterion. Our analysis did not capture instances of multiple first or corresponding authors (equally contributing authors) and used author position as a proxy for mentor–mentee relationships. Presumed author sex might not reflect author

gender, which might be a relevant distinction in our analysis. Our analysis also focused on experimental and reporting standards proposed by the NIH, which were not exhaustive.

CONCLUSIONS

Women's involvement in preclinical cardiovascular research is positively associated with considering sex as a biological variable, which is a practice that is expected to inform and promote advances in women's health. Researcher sex is not associated with other measures of experimental rigor or research impact. Limited mentorship opportunities may be contributing to women's underrepresentation in this field.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In this analysis of 3,396 preclinical studies in 5 leading cardiovascular journals, female authorship was positively associated with considering sex as a biological variable, but not with other measures of methodological rigor or 60-month citation counts. Over a 10-year period, the proportion of studies with first and senior authors of differing sex was low and stable, suggesting that segregation by sex in mentorship relationships exists and persists. These data indicate that women's underrepresentation in preclinical cardiovascular research is not due

to differences in research capacity or impact. Limited mentorship opportunities for women in preclinical cardiovascular research may be an important contributor.

TRANSLATIONAL OUTLOOK: Further study to identify and understand barriers to women's involvement in preclinical cardiovascular research is warranted. Enhancing mentorship opportunities for women should be explored as a potential strategy to improve the status quo.

REFERENCES

1. Ramirez FD, Motazedian P, Jung RG, et al. Sex bias is increasingly prevalent in preclinical cardiovascular research: implications for translational medicine and health equity for women: a systematic assessment of leading cardiovascular journals over a 10-year period. *Circulation* 2017;135:625-6.
2. Clayton JA, Collins FS. Policy: NIH to balance sex in cell and animal studies. *Nature* 2014;509:282-3.
3. Beery AK. Inclusion of females does not increase variability in rodent research studies. *Curr Opin Behav Sci* 2018;23:143-9.
4. Klein SL, Schiebinger L, Stefanick ML, et al. Opinion: sex inclusion in basic research drives discovery. *Proc Natl Acad Sci U S A* 2015;112:5257-8.
5. Rotenstein LS, Jena AB. Lost Taussigs - the consequences of gender discrimination in medicine. *N Engl J Med* 2018;378:2255-7.
6. Nielsen MW, Alegria S, Borjeson L, et al. Opinion: gender diversity leads to better science. *Proc Natl Acad Sci U S A* 2017;114:1740-2.
7. Asghar M, Usman MS, Aibani R, et al. Sex Differences in authorship of academic cardiology literature over the last 2 decades. *J Am Coll Cardiol* 2018;72:681-5.
8. Soklaridis S, Zahn C, Kuper A, Gillis D, Taylor VH, Whitehead C. Men's fear of mentoring in the #MeToo era - what's at stake for academic medicine? *N Engl J Med* 2018.
9. Valantine HA, Collins FS. National Institutes of Health addresses the science of diversity. *Proc Natl Acad Sci U S A* 2015;112:12240-2.
10. Ramirez FD, Motazedian P, Jung RG, et al. Methodological rigor in preclinical cardiovascular studies: targets to enhance reproducibility and promote research translation. *Circ Res* 2017;120:1916-26.
11. Wren JD, Kozak KZ, Johnson KR, Deakyne SJ, Schilling LM, Dellavalle RP. The write position. A survey of perceived contributions to papers based on byline position and number of authors. *EMBO Rep* 2007;8:988-91.
12. Lariviere V, Desrochers N, Macaluso B, Mongeon P, Paul-Hus A, Sugimoto CR. Contributorship and division of labor in knowledge production. *Soc Stud Sci* 2016;46:417-35.
13. Ceci SJ, Ginther DK, Kahn S, Williams WM. Women in academic science: a changing landscape. *Psychol Sci Public Interest* 2014;15:75-141.

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