# Sex-Related Reporting in Randomized Controlled Trials in Medical Journals

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## ABSTRACT

**A historical bias towards homogeneous male populations in biomedical research has often left the variable of sex under-addressed or unexplored entirely. While advocates such as the NIH and European Commission have worked towards correcting this imbalance by mandating the inclusion of women in scientific research, this has not translated into research analysis and reporting of outcomes by sex in clinical trails. A review was conducted of randomized controlled trials (RCTs) published in *The Lancet* and *The New England Journal of Medicine* (*NEJM*), between April 1, 2016, and July 16, 2016. Across 54 trials that reported the breakdown by sex of the study sample, 41% of participants were female, representing improvement throughout the past decade while recognizing existing disparity. Further, the inclusion of women was not linked to meaningful analyses of outcomes by sex: no trial had a prespecified analysis of differences by sex, and 57% of trials did not include sex-specific analyses of any sort. While women may be increasingly included in medical research, any differing outcomes between male and female participants are not being appropriately analysed and reported. The action of medical journals, editorial associations, and advocacy is imperative to correct this sex schism in biomedical research. Funders and editors must commit to requiring the disaggregation of data by sex, gender, or both, so that researchers, clinicians, and policy makers are better able to understand the sex and gender-specific outcomes of trials of clinical and global health interventions.**

That women and men have different physiology, experiences of illness, and health-care outcomes is well established.[1] From the benefits of aspirin for prevention of cardiovascular events[2] to the effects of sleep medication,[3] sex differences in health outcomes, and in the most appropriate health-care interventions, matter to doctors and patients. Despite this knowledge, a historical bias towards homogeneous male populations in biomedical research has often left the variable of sex under-addressed or unexplored entirely.

Advocates have worked towards correcting this imbalance for many years. A milestone in this effort, the National Institutes of Health (NIH) Revitalization Act, passed in 1993 and amended in 2001, mandates appropriate inclusion of women, as well as minority groups, in all NIH-funded research.[4] Several other major funders have since taken up similar positions: the European Commission, the Irish Research Council, and the Canadian Institutes of Health Research, for example, all call for the inclusion of women in scientific research.[5–7] As Clayton and Tannenbaum have recently argued,[8] if results for male and female participants are not analyzed separately, aggregate results may mask important clinical differences in the effects of interventions, toxicity, symptoms, or adverse effects. But is the inclusion of women upheld by researchers? Do these guidelines translate into researchers analyzing and reporting sex-related outcomes?

To answer this question, we conducted a review of randomized controlled trials (RCTs) published in *The Lancet* and *The New England Journal of Medicine* (*NEJM*) between April 1, 2016, and July 16, 2016. Sixty trials were identified, excluding nine that were sex-specific (focusing on clinical topics such as preterm delivery or in-vitro fertilization). We collected data on four main indicators: whether sex stratification was prespecified; the proportion of female participants included; whether sex-related results were reported; and whether a discussion of any or no sex-related findings was present. Across the 54 trials that reported the breakdown by sex of the study sample, 41% of participants were female. This represents improvement

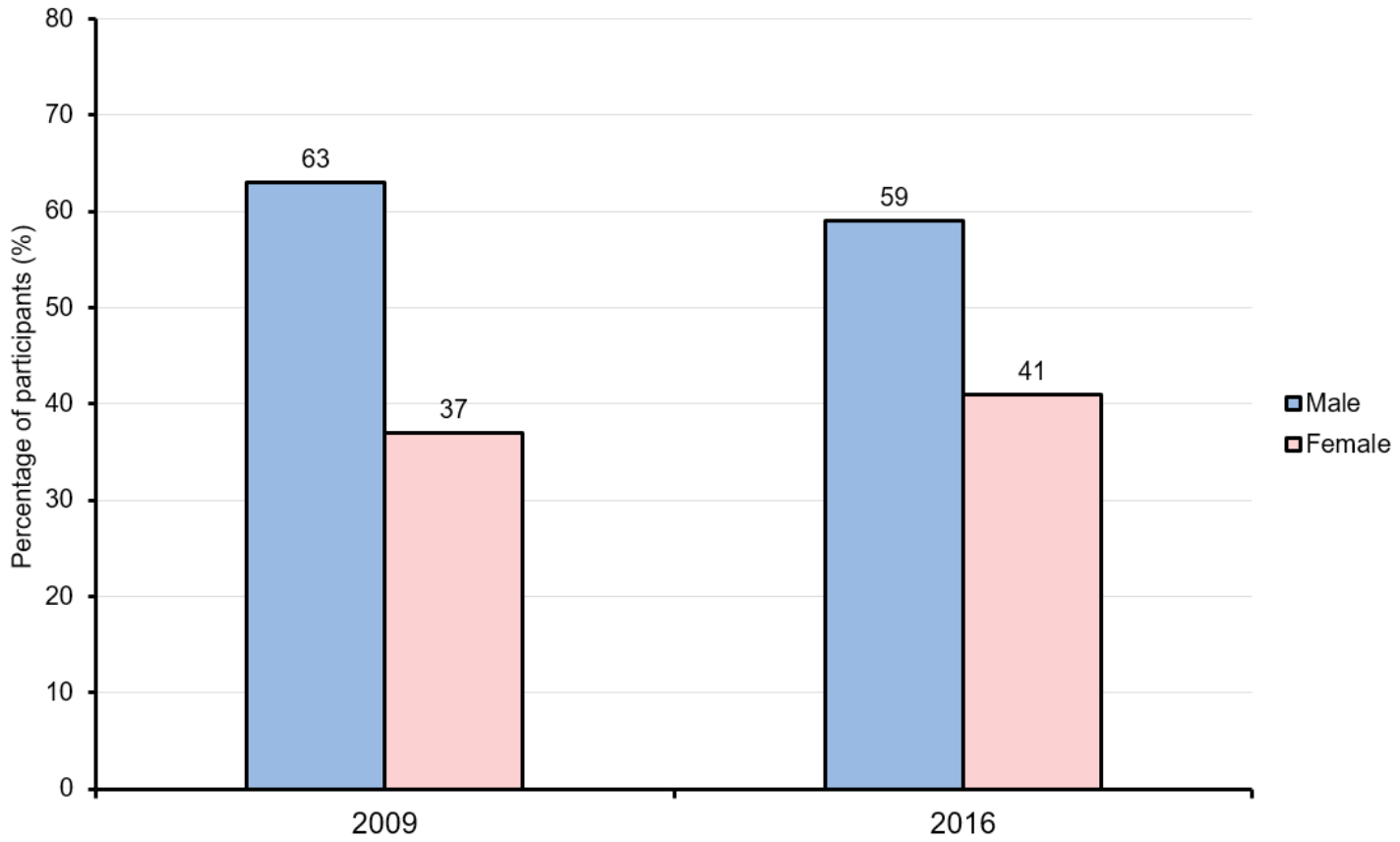


Figure 1: Proportion of male and female participants in randomised controlled trials. In 2009, 37% of RCT participants were female.[9] The present study finds a modest rise in female participation, with 41% of participants being female. Female participation still falls short of representing the 50% of the world's population that is female.

throughout the past decade: in 2009, a sampling of trials found the average proportion of female participants to be just 37%[9] (depicted in Figure 1). However, this modest rise in female participation still falls short in representing the almost 50% of the world's population that is female.

Further, the inclusion of women was not linked to meaningful analyses of outcomes by sex. No trial had a prespecified analysis of differences by sex. As depicted in Figure 2, a striking 34 (57%) of the 60 RCTs did not include sex-specific analyses of any sort, with six (10%) articles not even reporting the number and proportion of men and women in the trial report. Just 29 (48%) of the trials published reported sex-related analyses in the results section. Only three (5%) of the 60 RCTS noted the results of any sex differences in the discussion section. Thus, while women may be increasingly included in medical research, any differing outcomes between male and female participants are not being appropriately analyzed and reported. Similarly, a previous review of RCTs in major medical journals to 2013 found that although most studies included women, only 22% analyzed sex or gender differences and of these not one discussed significant or no sex-specific findings.[10]

Journals have ample opportunity and considerable leverage to bolster their requirements. Some major medical journals, including The *BMJ* and the *NEJM*, require only that authors report the sex distribution of participants and make no request for sex-specific analyses, prespecified or post-hoc. *JAMA* instructs authors to "report the sex distribution of study participants or samples in the Methods section." If only one sex is reported or included in the study, authors are instructed to "explain why the other sex is not reported or included, except for studies of diseases and disorders that only affect males (e.g., prostate disease) or females (e.g., ovarian disease)." *The Lancet* explicitly encourages, but does not require, researchers to "enroll women and ethnic groups into clinical trials of all phases, and to plan to analyze data by sex and by race." Journals' encouragement is a step in the right direction, but, as evidenced by our review, a stronger stance is necessary to push researchers to rigorously consider sex-specific results in the design and interpretation of their

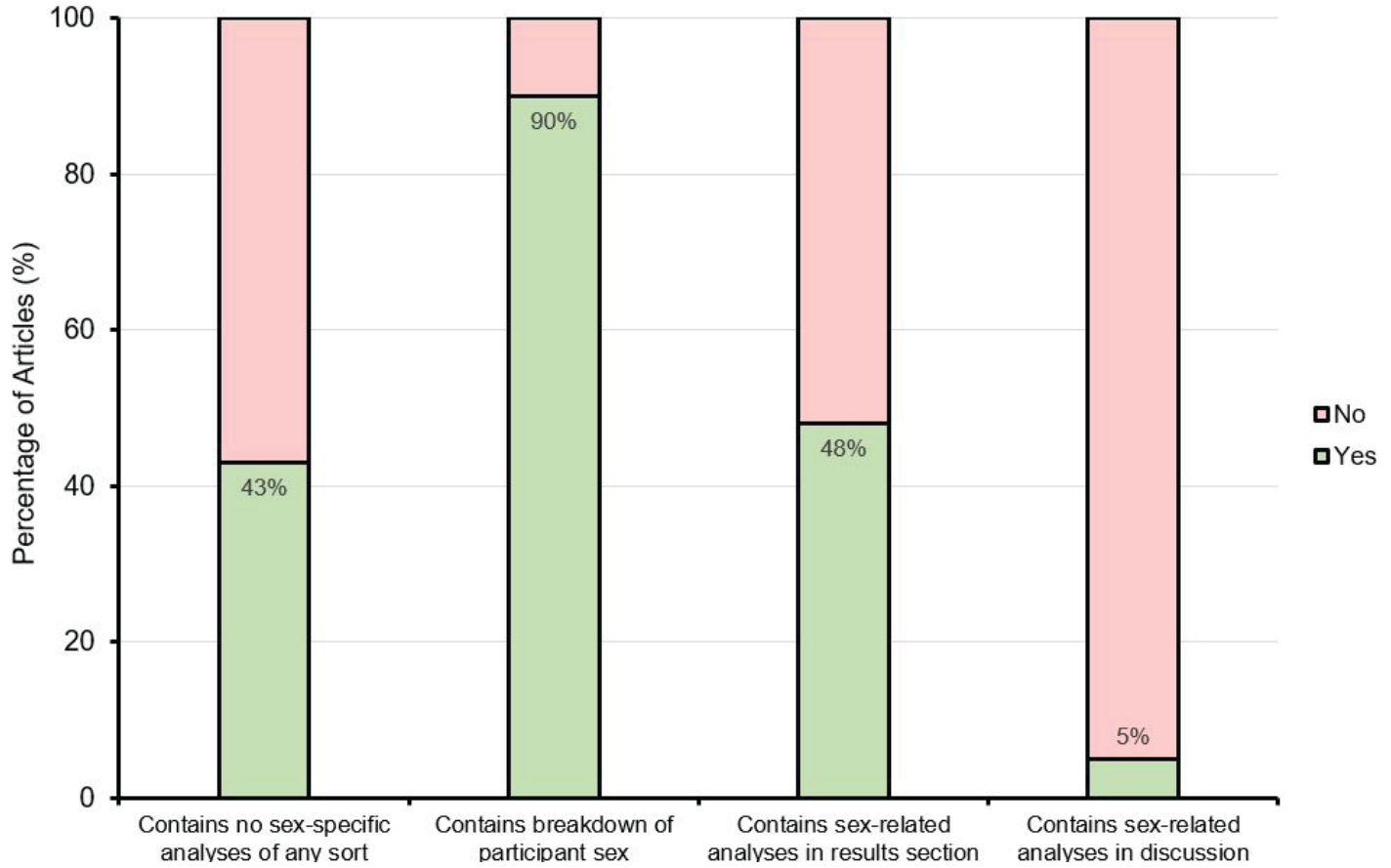


Figure 2: Degree of sex-specific analyses in 60 RCTs. Of the 60 RCTs considered in the present study, 34 (57%) do not include sex-specific analyses of any sort. Six (10%) articles do not report the number and proportion of men and women in the trial. Twenty-nine (48%) of trials report sex-related analyses in the results section. Only three (5%) of the 60 RCTs note the results of any sex differences in the discussion section. This finding suggests that differing outcomes between male and female participants are not being appropriately analysed and reported.

trials.

Editorial associations and guidelines, too, have so far underused their potential to shape medical research and reporting in this area. The recommendations of the International Committee of Medical Journal Editors (ICMJE) for the conduct, reporting, editing, and publication of scholarly work in medical journals, which many medical journals endorse, indicate that "separate reporting of data by demographic variables, such as age and sex… should be routine, unless there are compelling reasons not to stratify reporting, which should be explained." Yet, these recommendations do not require that this separate reporting be accompanied by analyses that were pre-planned, much less sufficiently powered. Similarly, the leading reporting guideline for clinical trials, CONSORT, requires only the "generalizability" of results to be assessed and addressed in an article's results and discussion sections, but sex is not mentioned as a factor for which this generalizability must be considered.

To hold researchers, funders, journals, and editorial associations accountable, the continued presence of advocacy groups is vital. To keep the issue of sex-specific reporting at the forefront of medical research, initiatives such as Women in Global Health, the Lancet Commission on Women and Health,[11] and the Harvard Women and Health Initiative, among others, have urged medical journals and funders to mandate that research studies enroll women and publish findings disaggregated by sex. In 2014, the National Women's Health Network in the USA pressed the Food and Drug Administration to create its 2014 Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data, including sex.[12] Others have argued that not just sex but gender must be reported to have a full understanding of relevant differences between individuals and groups.[8]

Funders and editors must commit to requiring the disaggregation of data by sex, gender, or both, so that researchers, clinicians, and policy makers are better able to

understand the sex and gender-specific outcomes of trials of clinical and global health interventions. Mandatory requirements in turn allow meta-analyses to achieve the necessary power to draw statistically meaningful conclusions about sex-specific responses to interventions, allowing the medical community to tailor health care to meet the needs of all people.

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