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Sex Bias Exists in Human Surgical Clinical Research

Neel A. Mansukhani, MD[1], **Dustin Y. Yoon, MD, MS**[1], **Katherine A. Teter, MD**[1], **Vanessa C. Stubbs, MD**[1], **Irene B. Helenowski, PhD**[1], **Teresa K. Woodruff, PhD**[2,3], and **Melina R. Kibbe, MD**[1,3]

[1]Department of Surgery, Northwestern University, Chicago, IL, USA

[2]Department of Obstetrics and Gynecology, Northwestern University, Chicago, IL, USA

[3]Women's Health Research Institute, Northwestern University, Chicago, IL, USA

Abstract

Importance—Sex is a variable that is poorly controlled for in clinical research.

Objective—Determine if sex bias exists in human surgical clinical research, determine if data are reported and analyzed using sex as an independent variable, and identify specialties where the greatest and least sex biases exist.

Design—Review and data abstraction from published peer-reviewed manuscripts.

Setting—All original peer-reviewed manuscripts published in 2011 and 2012 in Annals of Surgery, American Journal of Surgery, JAMA Surgery, Journal of Surgical Research, and Surgery.

Main Outcome Measures—Study type, location, number and sex of subjects, sex matching, and inclusion of sex-based reporting, statistical analysis, and discussion of data.

Results—Of 2,347 articles reviewed, 1,668 included human subjects. After excluding 365 articles, 1,303 manuscripts remained: 17 (1%) included only males, 41 (3%) included only females, 1,020 (78%) included males and females, and 225 (17%) did not document the sex of the subjects. While females represent over 50% of the total number of subjects included, considerable variability existed with the number of male, female, and unspecified subjects included among the journals, between US domestic and international studies, and between single versus multi-center studies. For manuscripts included in the study, only 38% reported these data by sex, 33% analyzed these data by sex, and 23% included a discussion of sex-based results. Sex matching of the subjects included in the research was poor, with only 18% of the studies matching the inclusion of both sexes by 80%. Upon analysis of the different surgical specialties, a wide variation in sex-based inclusion, matching, and data reporting existed, with colorectal surgery having the best matching of males and females and cardiac surgery having the worst.

Conclusion—Our data show that sex bias exists in human surgical clinical research. Few studies included men and women equally, less than one-third performed data analysis by sex, and there was wide variation in inclusion and matching of the sexes among the specialties and the journals

Corresponding Author: Melina R. Kibbe, MD, Division of Vascular Surgery, Northwestern University, 676 N St. Clair, Suite 650, Chicago, IL 60611, Office: (312)503-6701, Fax: (312)503-4617, mkibbe@northwestern.edu.

reviewed. Because clinical research serves as the foundation for evidence-based medicine, it is imperative that this disparity be addressed so that therapies benefit both sexes.

INTRODUCTION

In 1977, the Food and Drug Administration (FDA) barred women of "childbearing potential" from participating in clinical research until adequate safety and efficacy information could be developed during animal and early clinical studies.[2] This act, along with perceived challenges with recruiting women, subsequently resulted in the poor inclusion of women in clinical trials.[3,4] In addition, female subjects have been historically regarded as suboptimal research subjects due to the estrous cycle and inherent reproductive differences from males, even though data exist to refute this assumption.[5,6] Due to the low enrollment of women in clinical trials, the National Institutes of Health (NIH) Revitalization Act was introduced and signed into law in 1993. This law mandated the inclusion of women as subjects in clinical research funded by the NIH. However, recent studies have shown that the inclusion of women in clinical trials has only marginally improved.[7,8,9]

The equal inclusion of men and women in clinical trials is important as exemplified by the drug zolpidem (AmbienR), a sleep aid medication. Zolpidem was originally approved by the FDA in 1992. In the New Drug Application submitted to the FDA, it was documented that the peak drug concentration after administration was 45% higher in females, yet the drug was approved for the same dose in both males and females.[10] In 2013, it was uncovered that some women taking zolpidem were involved in automobile accidents the next morning.[11] Investigation revealed that women metabolized the drug more slowly than men.[12] This led to a label change approved by the FDA in May 2013, recommending that women take half the dose as men.[13] It is currently unknown how many other drugs may be metabolized differently by sex, or simply work differently in males and females. However, the Government Accountability Office (GAO) performed an assessment of adverse events by sex and reported that 8 out of 10 drugs removed from the market by the FDA were due to adverse events in women.[14] It is well known that males and females experience health and disease differently, metabolize and respond to some drugs differently, respond to medical devices differently, and can have different outcomes following medical interventions.[15–24]

Surgical research is not immune to this problem. We recently demonstrated that significant sex bias exists in surgical biomedical research.[25] Based on this study and pressure from the advocacy community, the NIH announced that sex must be considered as a variable in all NIH funded studies beginning January 2016.[26–28] It remains unknown if the same sex bias exists in human surgical clinical research. Males and females can have different postoperative outcomes, complication rates, and re-admission rates, so it is important to know if this problem of sex bias is pervasive in surgery.[29–33] Adequately controlling for sex as a variable with inclusion, data reporting, and data analysis is important as data derived from clinical research serve as the foundation for evidence-based medicine. Thus, the objective of this study was to determine if sex bias exists in human surgical clinical research, and to identify areas where the greatest and least sex biases exist. We hypothesize that males and females are not included in surgical clinical research in equal numbers, and that data are not reported or analyzed using sex as an independent variable.

METHODS

Data Abstraction

Data were collected as previously described by Yoon et al.[25] All original manuscripts published from January 1, 2011 through December 31, 2012 in the top five ranked American non-specialty surgical journals which publish internationally and across specialties were reviewed. These journals include *Annals of Surgery, American Journal of Surgery, JAMA Surgery, Journal of Surgical Research, and Surgery*. Only original peer-reviewed research articles were included in the study. Articles excluded from data abstraction were review articles, letters to the editor, case reports etc. Of the original peer-reviewed research articles, articles were further excluded if they included any animal or cell data, the number of included subjects was zero or not stated, or the article studied anatomically sex-specific disease (e.g. ovarian, testicular, prostate etc.).

Variables abstracted

The following data were abstracted: type of study (i.e. animal, cell, or human), single or multi-center study, domestic or international study, whether the manuscript studied a sex specific disease by anatomic criteria such as prostate, ovarian, cervical etc., the number and sex of each subject studied (if specified), and presence of sex-based data reporting. When stratifying for sex-based reporting, articles were assessed for sex-based reporting of data, analysis of data by sex, and inclusion of sex-based results in the discussion section. Finally, surgical sub-specialty responsible for each study was noted. Specialties in which <10 articles were published over the 2-year study period were marked as “other”.

Matching of included subjects by sex

The degree of sex matching for the subjects included within each study was calculated. The number of included males and females was considered and the lesser number of subjects (male or female) in an individual study was defined as the numerator, and the greater number of subjects (male or female) was defined as the denominator for individual studies. The percent matching of males and females included as subjects was calculated as the ratio of the numerator/denominator multiplied by 100. For example, a 100% match of male and females would include 50 males and 50 females as subjects. The equation would equal $50/50 \times 100 = 100\%$. A 50% matching of male and female subjects would include 50 males and only 25 females, with the equation equal to $25/50 \times 100 = 50\%$.

Statistical analysis

Chi-squared tests were employed to examine differences between publications by journal which stated or did not state sex, to compare the numbers of males, females, and unspecified sex subjects in the studies presented in each journal, between domestic and international manuscripts, and between manuscripts published by the different specialties. The differences in the distribution of sex matched subjects, sex-based reporting, analysis, and discussion of the data by specialty were also assessed using a chi-squared test. Significance was assumed for $p < 0.05$. Analyses were conducted using SAS version 9.4.

RESULTS

Sex of human subjects is often unstated

In total, 2,347 publications were reviewed among all five surgery journals. Of these, 1,668 (71%) included human subjects. 365 publications were excluded because they included animals or cells, studied a sex-specific disease, or did not report the number of subjects included. Of the 1,303 manuscripts reviewed (Table 1), 1,078 (83%) stated the sex of subjects included in the study, while 225 (17%) did not state the sex of subjects included (Figure 1A). While the pattern of this finding was consistent among all five journals (Figure 1B), the distribution of these differences were statistically significant. The *American Journal of Surgery* had the most subjects with the sex not stated (26%) while *Annals of Surgery* had the least (8%, p<0.0001). Of the 1,078 manuscripts that stated the sex of the subjects, 17 (1.6%) were male only studies, 41 (3.8%) were female only studies, and 1,020 (94.6%) included males and females (Figure 1C, p<0.0001). These data were similar between US domestic and international studies. Of the 771 US domestic publications that stated the sex of the subjects, 1.6% were male only, 4.3% were female only, and 94.1% included males and females. Of the 532 international publications that stated the sex of the subjects, 1.5% were male only, 3.1% were female only, and 95.4% included males and females.

Sex-based reporting, analysis, and discussion of data

Of all studies included, only 38% reported data separately for male and female subjects, only 33% performed statistical analysis on data collected by sex, and only 23% of articles addressed sex-based results in the discussion section (Figure 2). These data were similar between domestic (37%, 32% and 23% respectively) and international studies (40%, 35%, and 23% respectively). Between specialties, these data were highly variable. For example, endocrine surgery, surgical oncology, colorectal, and thoracic surgery were the highest performers in sex-based data reporting, analysis, and discussion of the data (Supplemental Table 1, p<0.0001). Breast, bariatric, and cardiac surgery were the lowest performers in sex-based data reporting, analysis, and discussion of the data (p<0.0001).

Disparity exists with the absolute number of male and female subjects studied

In total, over two years and among the five journals studied, 115,377,213 human subjects were included in the published manuscripts. There were 46,111,818 (40%) males, 58,805,665 (51%) females, and 10,459,730 (9%) unspecified subjects (Figure 3A). After excluding manuscripts on which veterans and surgical trainees were the subjects, the sex of subjects included were similar: 40% male, 51% female, and 9% unspecified. An analysis of manuscripts publishing on cardiac and thyroid disease, which are known to be more prominent in women, revealed that the sex of subjects included were 25% male, 59% female, and 16% unspecified. The total number of males, females, and unspecified subjects between journals was highly variable (Figure 3B, p<0.0001). For example, there were 15%, 22%, and 63% males, females, and unspecified subjects, respectively, in the *American Journal of Surgery*, but 46%, 52%, and 2% males, females, and unspecified subjects, respectively, in *Surgery*. Similarly, differences were detected between US domestic and international studies. In US domestic studies there were 40%, 51%, and 9% male, female, and unspecified subjects, respectively, while in international studies there were 48%, 26%, and 26% male, female, and unspecified subjects, respectively (Figure 3C, p<0.0001). In single-center studies, there were 46%, 51%, and 3% male, female, and unspecified subjects, respectively, while in multi-center studies there were 39%, 51%, 10% male, female, and unspecified subjects, respectively, (p < 0.0001).

Disparity in inclusion of subjects by sex exists between surgical specialties

There was inconsistency between surgical subspecialties in the number of male, female, and unspecified subjects included in the studies. Articles from trauma/critical care, pediatric, thoracic, and cardiac surgery had greater than 50% male subjects (Figure 3D, p<0.0001). Surgery-unspecified, endocrine, bariatric, and breast surgery had greater than 50% female subjects (Figure 3E, p<0.0001). Transplant, general surgery, and articles regarding surgical education and training had greater than 50% of unspecified subjects (Figure 3F, p<0.0001). Furthermore, there was a significant difference in overall distribution of male, female, and unspecified subjects by specialty (p<0.0001).

Studies do not match included subjects by sex

Among articles which included both males and females, only 2% of articles matched the sex of included subjects by 100% (Figure 4A). Only 45% of articles matched included male and female subjects by 50%. In comparing specialties, breast and cardiac surgery did not match any studies by 100%. Examination of the specialties that matched inclusion of males and females by at least 50% revealed that colorectal (p<0.0001), transplant (p<0.0001), pediatric surgery (p<0.0001), and surgical oncology (p<0.0001) contained the highest number of studies, while breast (p=0.0003), cardiac (p<0.0001), bariatric (p<0.0001) and surgical education (p<0.0001) contained the lowest number of studies. There was a significant difference in the overall distribution of 50% or greater matching across all specialties (p< 0.0001) (Figure 4B).

DISCUSSION

In this manuscript we show that significant sex bias exists in human surgical clinical research. Most importantly, of the manuscripts reviewed only approximately one-third of manuscripts statistically analyzed and reported the data by sex. These data were consistent in comparing domestic and international studies, and after excluding surgical education and VA studies, the latter of which is predominantly male. Furthermore, the sex of the subjects included in the research was not stated in 17% of published peer-reviewed studies. Of those manuscripts that stated the sex of the subjects, 95% included both males and females. While females represent over 50% of the total number of subjects included in the clinical research studies, considerable variability existed with the number of male, female, and unspecified subjects included among the journals, between US domestic and international studies, and between single versus multi-center studies. The proportions of male, female, and unspecified subjects was unchanged with the exclusion of studies conducted at the VA and on surgical trainees. There was also wide variability in the number of male, female, and unspecified subjects included among the surgical specialties. Finally, sex matching of the subjects included in the research is practiced in less than half of the peer-review publications reviewed using a very liberal 50% matching criteria. Thus, the results of this study confirm our hypothesis that males and females are not included in human surgical clinical research in equal numbers, and that data are analyzed and discussed using sex as an independent variable in less than one-third of surgical clinical research studies

To our knowledge this is the largest and most comprehensive study to examine sex bias in human surgical clinical research. However, there are a few studies in other disciplines that examine sex bias in clinical research. The data presented in our study shows an improvement compared to the data published by Kwiatkowski et al who showed that in cancer trials more men (59.8%) were included than women.[34] Meinert et al showed that for clinical trials published in United States journals from 1966–1998 the percent of subjects by sex included: males and females (55%), males only (12%), females only (11%), and unspecified sex (21%).[7] Vidaver et al surveyed the medical literature from 1995–2000 and showed that less than 20–30% (depending on the year) of the studies analyzed data by sex.[35] Similarly, Blauwet et al showed that sex specific reporting of data was only 37% in general medical journals and 23% in cardiovascular journals, while Geller et al showed that outcomes were not reported by sex in 75% of federally funded randomized clinical trials published in 2009.[9,36] Finally, in a study of the orthopedic literature, Hettrich et al showed an increase in sex-specific analysis from 19% to 30% from 2000 to 2010.[37] These data are remarkable given that many diseases have a clear female prevalence.[38–44] Of note, our results are consistent with the US GAO report to the NIH in October 2015 which revealed that more females than males were included in NIH-funded clinical research from 2004–2015. In addition, our data on the lack of sex-based reporting and analysis is consistent with the US GAO's report and the Institute of Medicine's 2010 report on healthcare research. These later reports showed that despite the NIH Revitalization act of 1993 and increased female enrollment in clinical trials, sex-based reporting and analysis of results remains an area of disparity.[45,46] Despite good overall inclusion of females in human surgical clinical research, we were surprised to find the low rate of matching of subjects with regards to sex. Furthermore, we were surprised to find that the sex of the subjects included was still not reported in over 17% of peer-reviewed studies published in 2011 and 2012. Finally, the wide variation in sex-based data reporting and analysis between surgical specialties was surprising in that some specialties included sex-based data reporting and analysis in over 50% of published studies, while some specialties included sex-based data reporting and analysis in less than 10% of published studies. Together, our data imply that sex disparity exists in human surgical clinical research in many ways despite the government mandate of female inclusion in NIH-funded clinical trials.

Implications of these findings are numerous. First, drugs, therapies, and devices may be developed that are effective for only one sex.[47] Second, for therapies and drugs that are reported to have an overall low efficacy in men and women when the data is aggregated, the therapy or drug may be abandoned; however, that therapy or drug may have greater efficacy in one sex versus the other. This would only be known if sex-based analysis and reporting of the data was performed. For example, the Human Papilloma Virus vaccine is much more effective in women versus men.[48,49] But, in aggregate, the efficacy is low. If sex-based reporting of the data was not conducted, this therapy that is effective at preventing cervical papillomas in women may not have been developed. Third, therapies may be developed that have undesirable side effects in the opposite sex. For example, the odds of an adverse drug reaction in women is 50% greater than in men, women are more likely to be hospitalized due to an adverse drug reaction, and 80% of the drugs removed from the market by the FDA were due to undesirable side effects in women.[14,50,51] Thus, while it is important to aggregate data of both males and females, performing independent data analysis and reporting for both males and females can yield discoveries leading to valuable contributions to the health and wellbeing of males or females independently.

We acknowledge and understand that there are criticisms to including both sexes and accounting for sex differences in clinical research. [52–55] However, our recommendations are for an FDA mandate that requires drugs, devices, and new therapies to be tested equally in male and female subjects prior to market approval. Drugs which have been recalled due to adverse effects in one sex should be tested independently in both sexes as these drugs may be candidates for re-release with different dosing parameters for each sex. Research funding agencies such as the NIH, National Science Foundation, Department of Defense, the Veterans Affairs Administration, etc. should mandate researchers to match inclusion of males and females in clinical research, and report results independently for males and female subjects so that sex may be examined as in independent variable. Journal editors should require authors to include the sex of all subjects studied in published literature and require sex-based reporting, analysis, and discussion of data. In support of these views, the IOM recently published guidelines for sex-specific reporting of research.[56] Finally, government monitoring of sex-based inclusion of subjects, sex as an independent variable, and sex-based data reporting should be required, especially for research conducted using government funds. Such practices have been adopted by other countries and the U.S. should follow suit.[57]

Limitations exist within this study. Our study design was intended to capture a representative sampling of surgical clinical research, not a complete analysis of all surgical clinical research. The scope of this study was limited to manuscripts published in only five surgery journals over a two year period. These journals publish mainly on general surgery topics so there was a paucity of manuscripts from certain surgical sub-specialties such as neurological surgery, urology, orthopedic surgery, and plastic surgery. There was no inclusion or specification regarding the difference between sex and gender, and this study focused solely on the differences between phenotypic male and female sex.[58] Furthermore, these are observational data intended to highlight differences in inclusion, reporting, and analysis between sexes, and are not corrected for specific disease prevalence. Data capture for funding source was not consistent among the manuscripts; thus, we were not able to consistently and reliably discern if the research was funded and if it was funded by the NIH versus industry. Lastly, within the manuscripts analyzed for this study there were too few randomized controlled trials to develop meaningful conclusions; thus, we are conducting a separate study analyzing sex bias in all clinical trials registered with clinicaltrials.gov over a defined time period.

In conclusion, this study shows that sex bias exists in human surgical clinical research. Few publications included men and women equally, less than one-third performed data analysis by sex, and there was wide variation in inclusion and matching of the sexes between the specialties and the journals reviewed. Because clinical research serves as the foundation for evidence-based medicine, it is imperative that this disparity be addressed because therapies and practice derived from such studies may be specific to only one sex.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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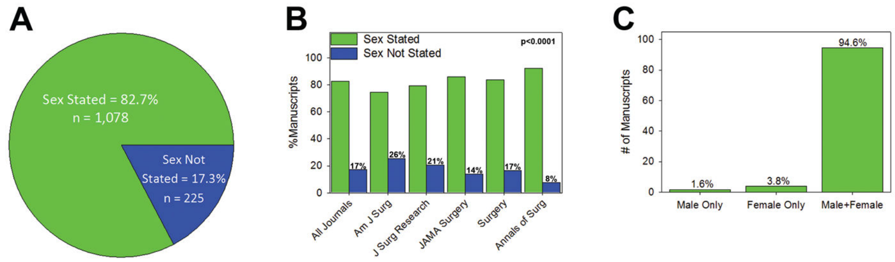

Figure 1. Sex of Subjects Included

Number and percent of manuscripts which state the sex of the human subjects included in (A) all manuscripts and (B) by journal. The distribution of rates of sex stated/not stated was different between journals (p<0.0001). (C) Number and percent of manuscripts that include male only, female only, and male and female subjects.

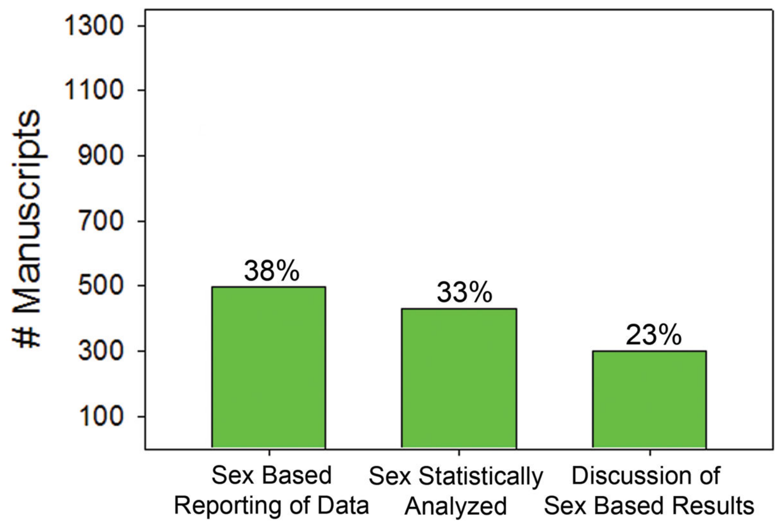

Figure 2. Sex-Based Data Reporting

(A) Percent of manuscripts that reported the data by sex. (B) Percent of manuscripts that statistically analyzed the data by sex. (C) Percent of manuscripts that included a discussion of the results by sex.

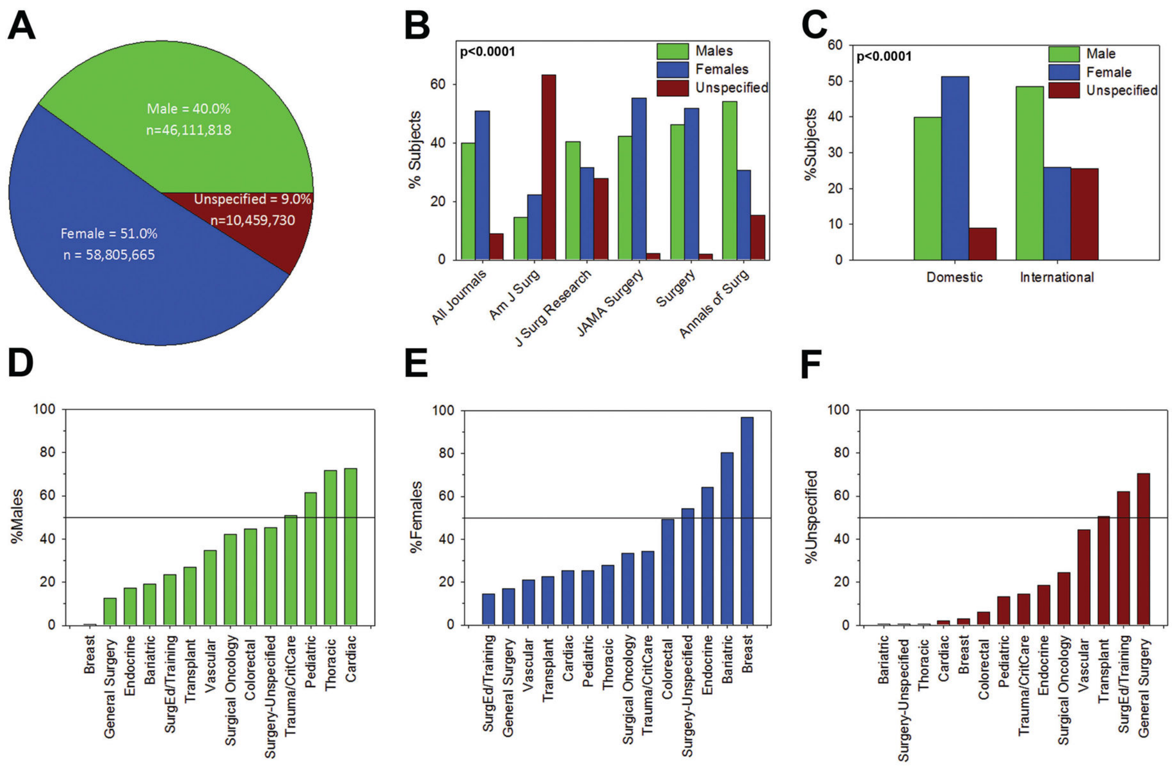

Figure 3. Number of Male and Female Subjects Included

Absolute number of male, female, and unspecified subjects included in (A) all manuscripts, (B) by journal, (C) in US domestic and international studies. Distribution of included males, females, and unspecified subjects between journals and between domestic and international studies was different (p<0.0001). (D) Number of male subjects included by specialty. (E) Number of female subjects included by specialty. (F) Number of unspecified subjects included by specialty. Distribution of included males, females, and unspecified subjects was different by specialty (p<0.0001).

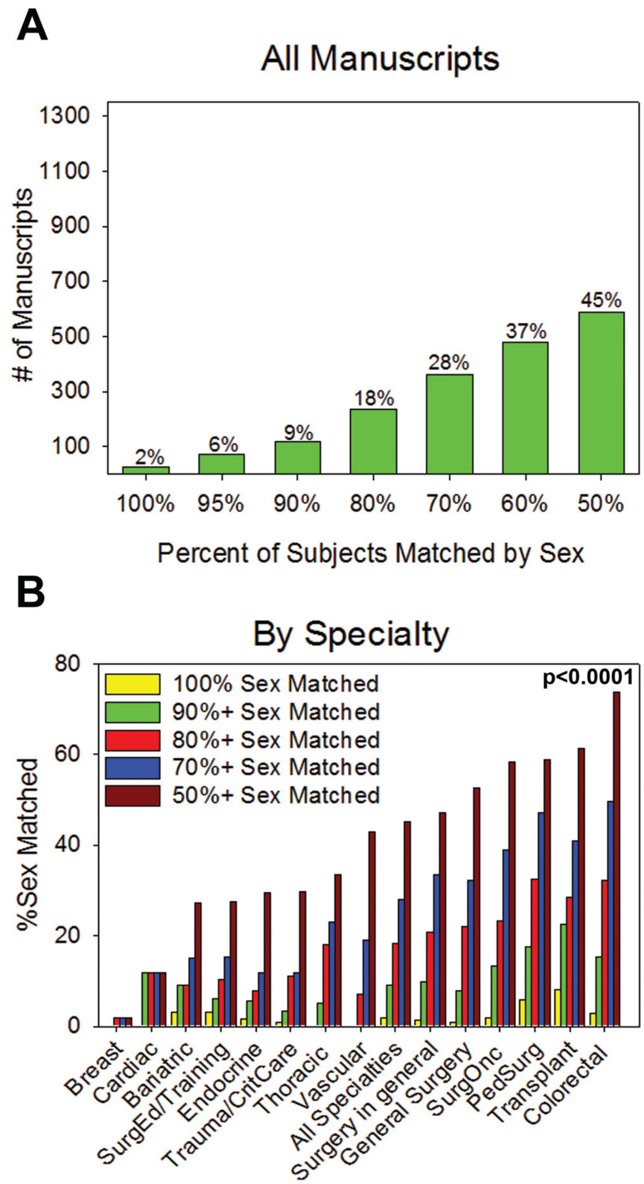

Figure 4. Sex Matching of Subjects

(A) Degree of sex matching in all manuscripts and (B) by specialty. There is a statistically significant difference in distribution of 50% or greater matching across all specialties ($p<0.0001$).

Author Manuscript

Author Manuscript

Author Manuscript

Table 1

Characteristics of all articles included across journals, centers, and specialties.

	# Manuscripts (%)
Total	1303
Journal	
American Journal of Surgery	392 (30.1%)
Journal of Surgical Research	116 (8.9%)
JAMA * Surgery	256 (19.6%)
Surgery	266 (20.4%)
Annals of Surgery	273 (21.0%)
Single & Multi Center	
Single Center	916 (70.3%)
Multi Center	387 (29.7%)
Domestic & International	
Domestic	771 (59.2%)
International	532 (40.8%)
Surgical Specialty	
Bariatric	33 (2.5%)
Breast	56 (4.3%)
Cardiac	17 (1.3%)
Colorectal	137 (10.5%)
Endocrine	126 (9.7%)
General Surgery	205 (15.7%)
Pediatric	34 (2.6%)
Surgical Education/Training	98 (7.5%)
Surgical Oncology	250 (19.2%)
Surgery – Unspecified	72 (5.5%)
Thoracic	39 (3.0%)
Transplant	49 (3.8%)
Trauma/Critical Care	118 (9.1%)
Vascular	42 (3.2%)
Other **	27 (2.1%)

* JAMA = Journal of the American Medical Association.

** Other includes biotech/biodesign (n=4), burn (n=2), neurosurgery (n=6), orthopedic surgery (n=2), healthcare disparities/EMR/epidemiology studies (n=8), otolaryngology/HNS (n=2), plastic surgery (n=1), urology (n=2).