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Sex Bias in Rhinology Research

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Abstract

Background—Analysis of general surgery literature has revealed noteworthy sex bias and underreporting. Our objective was to determine the prevalence of sex bias and underreporting in rhinology.

Methods—All articles in 2016 issues of *Rhinology*, *American Journal of Rhinology and Allergy*, and *International Forum of Allergy and Rhinology* were reviewed. 248 of 369 met inclusion criteria. Excluded studies were cadaveric, meta-analysis/review and editorial. Data collected included study type, demographics and sex-based statistical analysis.

Results—There were 202 clinical and 46 basic science/translational studies. Of 188/202 clinical studies with known sex, one included participants of a single sex. Sex matching >50% (SM₅₀) was found in 81.9%, and 55.9% performed sex-based statistical analysis. Domestic clinical studies performed sex-based analysis more frequently than international (54.9% vs 44.4%) and exhibited a higher rate of SM₅₀ (84.5% vs 80.3%), though these differences were not statistically significant. For basic/translational studies, 54.5% (24/44) provided sex breakdown. Among these, 29.2% included one sex, and 8.3% performed sex-based analysis. Of 10 using animals, 70.0% utilized one sex. The remaining 30.0% did not report sex. 0/4 cell line studies reported cell sex. 50.0% domestic and 56.3% international studies reported sex breakdown. 8.3% domestic and 3.1% international studies performed sex-based analysis.

Conclusions—While sex may impact outcomes, research without sex reporting and analysis is prevalent, particularly among basic science/translational studies. Future research must account for sex in demographics and analysis to best inform evidence-based clinical guidelines.

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Keywords

sex bias; biomedical research; humans; animals; cells; sexism; male; female; research design/ standards

INTRODUCTION

Sex as a biological variable

In an era characterized by individualized, patient-centered and “personalized” medicine there is increasing interest in the discovery and application of clinically significant biological differences between sexes, races, ethnicities, environmental exposures, genetic and epigenetic markers and more. In clinical practice sex is perhaps the most basic yet important initial distinction to consider. Well-known differences exist between the male and female sexes in the realm of health care and, in many cases, are critical in clinical decision-making.

Males and females may differ in disease prevalence and risk, drug metabolism and response to procedures and devices. For example, autoimmune diseases are more common in females, Parkinson’s disease is more common in males, and women are more susceptible to pain than men.¹ Adverse drug reactions (ADRs) are higher in females than males overall.² A striking 80% of prescription drugs withdrawn from the market between 1997 and 2001 were removed due to differences in life-threatening ADRs in women.^{3–4} Even after accounting for body weight some drugs exhibit sex-based differences in pharmacokinetics and toxicity, suggesting that other sex-related factors contribute to drug response.⁵ A classically cited example is zolpidem tartrate, a sedative drug prescribed as a sleep aid. After multiple women were involved in fatal motor vehicle accidents the day after taking zolpidem and it was discovered that females metabolize this drug more slowly, the United States FDA (Food and Drug Administration) required relabeling of zolpidem with a half-dose for females.^{6–7}

In the past female subjects have often been excluded from research endeavors due to concern for confounding effects from physiologic differences, ease of access to animals of one sex over the other, or ignorance of the importance of sex.^{8–10} However, because there are clinically significant, evidence-based biological distinctions between the sexes, arguments have been made that is imperative to include participants of both sexes, analyze data by sex, and publish outcomes stratified by sex in human, animal and cell research.¹¹

Attempts to address sex in health research

The National Institutes of Health (NIH) Revitalization Act of 1993 required all NIH-funded studies to include female and minority participants, and other federal and foreign agencies such as the Canadian Institutes of Health Research and the European Commission subsequently enacted similar requirements. Despite this legislation, a 2015 review of 48 health journals showed that many journals provide only recommendations, not requirements, for subject sex reporting in manuscripts. Specifically, in the 31 journals publishing human-only research, 11 (35.5%) lacked a sex reporting policy.³

Since this 1993 legislation sex reporting and bias, defined as underinclusion of one sex and/or lack of sex-based data analysis, in human clinical research has marginally improved. Beery et al 2011 reviewed multiple human research journals over time and found that approximately 32–45% of publications from 1949 to 1989 studied both sexes, followed by an improvement to >60% in 1999 and 2009. Sex-unspecified publications decreased from >20% in 1949 to 1979 to approximately 7% between 1989 and 2009.¹² However, disparities in sex reporting and particularly sex-based analysis persist in clinical research. Another 2011 study demonstrated that 75% of 86 human research articles with federal funding did not perform sex-based data analysis.¹³

Recent landmark analyses of the clinical surgery literature have also revealed significant sex bias and sex underreporting in surgical research. One large review of 1303 human subject studies in five general surgery journals in 2011–2012 revealed that 17.3% of studies did not report participant sex, less than half exhibited at least 50% subject sex matching, and only 33% analyzed data by sex.¹⁴ A similar analysis of high-impact Orthopedic Surgery journals reported minimal improvement in sex-based analysis in recent years, from 19% in 2000 to 30% in 2010.¹⁵

While sex bias in clinical research may be gradually improving, basic and translational science publications have failed to follow a similar pattern. The 1993 NIH legislation affected only female participation in clinical trials without mandating inclusion of female animals or cells in basic science/translational research.¹⁶ A 2009 study showed that approximately 80% of rodent studies in multiple biology disciplines were still using only male animals, which is almost identical to sex statistics in animal studies in 1990.¹² A recent large review of five surgery journals analyzing basic science (animal and cell) research similarly found that 32% of studies did not report animal or cell sex; when sex was reported 80% included males only.¹⁷ Thus, sex bias in animal studies is significant and has demonstrated minimal improvement over a 20-year period.¹⁸

Sex in Otolaryngology and Rhinology Research

Limited data exist regarding sex bias in otolaryngology research. A study of 210 basic science and preclinical publications from 2010–2015 on noise-induced hearing loss showed that 33% of studies did not report the total number of animal subjects. Almost two-thirds used only male animals and only 25% studied both sexes.¹⁹ This otology study is the only published analysis of sex bias to date in the otolaryngology literature.

Inclusion of males and females as well as sex reporting and sex-based data analysis are essential to most accurately guide future evidence-based guidelines in rhinology. To date neither rhinology nor the otolaryngology literature in general has been scrutinized for sex bias and reporting. As a result, we have no knowledge of how sex bias in this field compares to the general clinical and basic science literature. To our knowledge, this is the first study to analyze rhinology literature for sex reporting and disparity.

Objective

The goal of this study is to determine if sex bias and under-reporting exist in the current rhinology clinical, basic science and translational research and investigate the prevalence of sex-based statistical analysis in the published literature for this subspecialty.

METHODS

Data Collection

All published original manuscripts in all 2016 issues of *Rhinology*, *American Journal of Rhinology and Allergy* (AJRA), and *International Forum of Allergy and Rhinology* (IFAR) were reviewed (Figure 1). These three peer-reviewed journals were selected due to their focus on rhinology research within the greater field of otolaryngology. Study types excluded from this analysis were cadaveric, meta-analysis/review, case report or small case series, editorial, practice/methods, and non-patient-centered studies. One of two reviewers performed data extraction for each manuscript. Text, figures and tables in each manuscript were reviewed for data collection.

Variables

Variables collected for each manuscript included study type (clinical, basic science, translational; human, animal, primary cells versus cell lines), study location (domestic versus international), single versus multi-center or database study, randomized controlled trial and subject demographics. Studies were examined for mention of human, cell or animal sex, providing sex breakdown, sex matching 50% (SM₅₀), sex-based statistical analysis, and presence of any statistically significant sex differences in results. SM₅₀ was defined as a subject sex ratio of greater than or equal to 0.5. This metric was used to assess whether there were at least half as many participants of one sex as the other in a study. The number of participants of the less represented sex was divided by the number of participants of the sex with more participants, and multiplied by 100 to obtain the sex matching (SM) percentage. SM₅₀ was chosen because it is identical to previously published statistical methods in general surgery literature, and therefore also facilitates comparisons of sex inclusion with this literature. It also represents a low standard of inclusion of both sexes in research, with a ratio of 1:2. Sex-based statistical analysis was defined as presentation of results separately for each sex in the manuscript text or in table/figure format.

Between sex and gender, “sex” is reported more frequently than “gender” as a demographic in clinical surgical research. This was the case in 100% of reviewed studies, none of which provided any discussion of the sex versus gender demographics in the studied patient populations. Therefore, the sex demographic was analyzed in this study.

Statistical analysis

Overall sex variables were reported and also stratified by study type and location. Differences in sex distribution and reporting were assessed using the chi-squared and student's *t*-test where appropriate. Statistical analysis was performed with Stata STATA 14.0 software (Stata Corporation, College Station, Texas).

RESULTS

A total of 369 articles from the three aforementioned journals were reviewed. 248 articles met inclusion criteria. Clinical studies comprised 202 of 248 (81.5%). Basic science studies – including animal, human cells/tissue, and cell lines – comprised 46 of 248 (18.5%).

Clinical Research

Participant Sex and Sex Matching—Subject sex was not specified in 6.9% (14/202) of studies. Of 188/202 (93.1%) studies that provided sex breakdown, one (1/188, 0.5%) included participants of a single sex (Table 1). There were 1,096,253 total participants in all studies; 631,012 (57.6%) male and 465,241 (42.4%) female. SM₅₀ was found in 154/188 (81.9%) studies.

Sex-Based Data Analysis—Sex-based statistical analysis was not performed in 48.0% (97/202). Of the 105 (52.0%) studies that included sex-based data analysis, 29 (27.6%) reported at least one statistically significant sex-based result. Studies published in IFAR demonstrated the highest rate of sex-based analysis and SM₅₀, though this difference was not statistically significant ($p=0.254$ and $p=0.808$, respectively).

Study Location—In the clinical research category there were 78 domestic and 124 international studies (Table 1). Sex breakdown was not provided in seven (9.0%) domestic and seven (5.7%) international studies. Domestic studies performed statistical analysis by sex more frequently than international studies and exhibited a higher rate of SM₅₀, though these differences were not statistically significant (Figure 2). Of the 188 clinical studies that provided sex breakdown, 32/71 (45.1%) domestic and 65/117 (55.6%) international studies did not perform statistical analysis by sex ($p=0.166$). Sex matching of at least 50% was not found in 11 (15.5%) domestic and 23 (19.7%) international studies ($p=0.054$).

Basic Science and Translational Research

Participant Sex and Sex-Based Data Analysis—Of 369 articles reviewed, 46 basic or translational research studies were identified (Figure 1). There were 48 total groups of subjects (animal, human cell/tissue, or commercial cell line), as two studies analyzed both human tissue/cells and commercial cell lines (Table 2). Four studies that analyzed three cell groups were analyzed separately. A breakdown of sex reporting and analysis by journal is provided in Table 3.

Sex breakdown was provided in 54.5% (24/44) animal and human cell/tissue studies. Of these 24 studies that reported subject sex, 7/24 (29.2%) included only one sex, and 2/24 (8.3%) performed sex-based data analysis. Of 10 studies (22.7%) using animal subjects, seven (70.0%) utilized only one sex animal. The remaining three (30.0%) animal studies did not report sex. Thus, 0% (0/7) of animal studies reporting sex used both sexes. Four (8.7%) cell studies used a total of 3 cell groups. None of these four publications reported cell sex.

Study Location—In the basic and translational science category there were 12 domestic studies and 32 international studies (Table 2). Six of twelve (50.0%) domestic studies and 18/32 (56.3%) international studies reported sex breakdown. Of studies reporting sex, one

(1/6, 16.7%) domestic study and one (1/18, 5.6%) international study performed sex-based data analysis.

DISCUSSION

In a 2001 statement the Institute of Medicine (IOM) noted that “being male or female is an important basic human variable that should be considered when designing and analyzing studies in all areas and at all levels of biomedical and health-related research,” and that failure to do so will lead to missed “opportunities to obtain a better understanding of the pathogenesis of disease and to advance human health.”²⁰ Furthermore, sex bias in research may be contributing to the rising irreproducibility in preclinical biomedical research as well as false conclusions and implementation of unsound clinical and pharmaceutical guidelines, thus potentially compromising optimal patient outcomes and safety.¹¹

Rhinology research is subject to the same sex reporting and analysis standards, and there are known clinically relevant sex differences in sinonasal anatomy and pathophysiology that make consideration of sex an important component of research in this field. A 2011 study demonstrated that there are noteworthy differences in nasal airflow between men and women.²¹ Temmel et al showed that women are more likely to experience URI-related olfactory loss.²² The prevalence of olfactory dysfunction is higher in men than women, hypothesized to be related to a protective effect of female hormone levels on olfactory neuron age-related deterioration.^{22–25} Several studies have shown that females with chronic rhinosinusitis (CRS) report poorer Health Related Quality of Life than males despite similar CRS disease severity.^{26–27} In addition to these examples there are likely many yet undiscovered pathophysiologic sex differences in the field of rhinology.

Rhinology research has not been included in past sex bias analyses, so the quantification and extent of this problem in the rhinology literature was unknown. This analysis of top peer-reviewed rhinology journals reveals subject sex underreporting and noteworthy lack of sex-based data analysis, which are most evident in basic science and translational research. However, these measures of sex bias are less frequent in rhinology literature overall compared to analyses of other surgical literature, namely the recent Yoon et al 2014 and Mansukhani et al 2016 general surgery reviews, the largest and most comprehensive analyses of sex disparity in surgical research to date.¹⁴ Subject sex was unspecified in only 6.9% of rhinology versus 17.3% of general surgery clinical manuscripts, with SM₅₀ in 81.9% vs 45.2% and sex-based data analysis in 52.0% vs 33.2% of clinical manuscripts, respectively. In animal research sex was unspecified in 30% of rhinology and 22% of general surgery manuscripts. Among those that specified sex, 100% rhinology and 97% general surgery publications used a single animal sex. For commercial cell line research, however, 0% rhinology and 24% general surgery manuscripts specified cell sex, though there were only four cell research manuscripts in the rhinology journals reviewed here.^{14,17}

This study also reveals a disparity in sex reporting and analysis when comparing domestic and international rhinology research. Domestic studies appear to exhibit overall less prevalent sex bias in clinical research but lower rates of sex reporting in basic science and

translational research, though these differences were not statistically significant in clinical research, and sample size for basic science studies was small.

While overall rhinology research may appear more conscious of sex reporting than general surgery literature, this difference is slight and does not negate the importance of acknowledging the existing sex bias and need for improvement in sex-based reporting and analysis in rhinology research. In fact, the frequencies of SM₅₀ and sex-based analysis in this study would be even lower if calculated with the total number of manuscripts in the denominator instead of the number that actually mention subject sex. As discussed previously, research has shown that some sinonasal diseases exhibit sex differences and nasal airflow and anatomy are not identical between males and females. Furthermore, there may be additional, currently unknown sex-based rhinologic disease and metabolic differences between the sexes that have clinically significant effects. More stringent reporting and analysis guidelines should be widely enacted and followed in rhinology research in order to discover these potential sex differences, conduct higher-quality research, and provide stronger and safer evidence-based, individualized care.

In response to many striking literature reviews revealing sex bias in clinical and basic science research and calls for new legislation, in January 2016 the NIH issued a mandate requiring that “sex as a biological variable will be factored into research designs, analyses, and reporting in vertebrate animal and human studies,” for all NIH funding proposals which extended requirements to animal studies and sex-based data analysis.²⁸ Notably cell research was not included. The scope of this requirement was limited to NIH funding proposals but was adopted by many medical journals that publish predominantly basic science/translational research. To date little data exist regarding the effect of this mandate on sex reporting and analysis in clinical research journals. Future studies should use the data presented in this study to analyze trends in sex reporting and sex-based data analysis after implementation of the new 2016 NIH guidelines. Such an analysis should be ideally performed at least three to four years after implementation, after new NIH-funded research studies subject to these guidelines have been published.

Finally, a discussion of the notable lack of strict sex-related regulations pertaining to cell research is necessary. The 2016 NIH guidelines for funding proposals only place requirements on human and animal research, yet in the vast majority of analyses, including this manuscript, the lack of sex reporting and analysis is most prevalent in cell research. Cell research often serves as the foundation of future animal, clinical and pharmaceutical studies and trials; therefore, it just as imperative to consider sex at the basic cell level in all research, including rhinology studies. Future guidelines must strengthen regulations surrounding cell research in addition to animal and human research endeavors.

CONCLUSIONS

Sex underreporting and lack of sex-based data analysis are prevalent in the existing rhinology literature, particularly among basic science/translational studies. Future clinical and basic science/translational research in rhinology, including research guidelines, should account for sex in both demographics and statistical analysis to ascertain clinically

significant sex differences and most accurately and safely guide evidence-based, patient-centered care.

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Figure 1.

Box diagram of the three journals reviewed in this study and articles included, which were classified as human/clinical or basic science/translational.

Figure 2. Prevalence of sex matching (SM₅₀) and sex-based data analysis in manuscripts from domestic versus international institutions.

Demographics and sex reporting and analysis for clinical research manuscripts in three major rhinology journals.

Table 1

Journal	Study Participants				Studies		
	Total	Males	Females	p-value	Sex not reported	SM ₅₀	Sex-based analysis
<i>Rhinology</i> (n=31)	26,861	12,834 (47.8%)	13,921 (51.8%)	0.894	1/31 (3.2%)	24/30 (80.0%)	16/30 (53.3%)
<i>AJRA</i> (n=65)	55,317	21,254 (38.4%)	24,932 (45.1%)	0.818	5/65 (7.7%)	48/60 (80.0%)	29/60 (48.3%)
<i>IFAR</i> (n=106)	1,025,424	596,924 (58.2%)	426,388 (41.6%)	0.798	8/106 (7.5%)	82/98 (83.7%)	60/98 (61.2%)
Total (n=202)	1,096,253	631,012 (57.6%)	465,241 (42.4%)	0.803	14/202 (6.9%)	154/188 (81.9%)	105/188 (52.0%)
Study Location							
Domestic (n=78)	936,819	552,358 (59.0%)	383,737 (41.0%)	0.800	7/78 (9.0%)	60/71 (84.5%)	39/71 (54.9%)
International (n=124)	170,783	78,654 (46.1%)	81,504 (47.7%)	0.962	7/124 (5.7%)	94/117 (80.3%)	52/117 (44.4%)

Table 2

Overview of study types, sex reporting and sex-based data analysis for basic science and translational research manuscripts in three major rhinology journals.

Study Type (n=46)	
Animal	10
Human Cells/Tissue *	34
Commercial Cell Lines *	4
Animal and Human Cell/Tissue Study Characteristics (n=44)	
No Reporting of Sex	20/44 (45.5%)
Single Sex Studies	7/24 (29.2%)
Sex-Based Analysis	2/24 (8.3%)
Study Location	
<i>Domestic</i>	12
No Reporting of Sex	6/12 (50.0%)
Single Sex Studies	2/6 (33.3%)
Sex-Based Analysis	1/6 (16.7%)
<i>International</i>	32
No Reporting of Sex	14/32 (43.8%)
Single Sex Studies	5/18 (27.8%)
Sex-Based Analysis	1/18 (5.6%)
Commercial Cell Line Study Characteristics (n=4)	
Studies Reporting Cell Line Sex in Manuscript	0 (0%)
Total # of Cell Lines	3
Cell Lines **	mucin-producing NCI-H292 cells
	MNSE
	HSNE

* Two studies included both human cells/tissue and cell lines. There were 48 total groups of subjects (animal, human cell/tissue, or commercial cell line) in 46 manuscripts.

** MNSE = murine nasal septal epithelium; HSNE = human sinonasal epithelium

Demographics and sex reporting and analysis for animal (top) and human cell/tissue (bottom) research manuscripts in three major rhinology journals. „Missing” indicates studies for which an animal/cell subject number was not reported.

Table 3

Journal	Total	# of Animals			Unknown	Sex Not Reported	# of Animal Subject Studies		Sex-Based Analysis
		Male	Female				Single Sex Subjects	Sex Subjects	
<i>Rhinology</i> (N=2)	46	26 (56.5%)	20 (43.5%)	0 (0%)	0 (0%)	0 (0%)	2 (100%)	0 (0%)	0 (0%)
<i>AJRA</i> (N=3)	60 <i>Missing</i> N=1	0 (0%)	60 (100%)	0 (0%)	0 (0%)	1 (33.3%)	2 (66.7%)	0 (0%)	0 (0%)
<i>IFAR</i> (N=5)	157	30 (19.1%)	69 (44.0%)	58 (36.9%)	2 (40%)	3 (60%)	0 (0%)	0 (0%)	0 (0%)
Total (N=10)	263 <i>Missing</i> N=1	56 (21.3%)	149 (56.7%)	58 (22%)	3 (30%)	7 (70%)	0 (0%)	0 (0%)	0 (0%)
Journal	Total	# of Human Cells/Tissue			Unknown	Sex Not Reported	# of Human Cell/Tissue Studies		Sex-Based Analysis
		Male	Female				Single Sex Subjects	Sex Subjects	
<i>Rhinology</i> (N=5)	167	94 (56.3%)	66 (39.5%)	7 (4.2%)	1 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
<i>AJRA</i> (N=12)	279 <i>Missing</i> N=2	110 (39.4%)	108 (38.7%)	61 (21.9%)	6 (50%)	0 (0%)	1 (8.3%)	0 (0%)	0 (0%)
<i>IFAR</i> (N=17)	435 <i>Missing</i> N=3	211 (48.5%)	169 (38.9%)	55 (12.6%)	9 (52.9%)	0 (0%)	1 (5.9%)	0 (0%)	0 (0%)
Total (N=34)	881 <i>Missing</i> N=5	411 (46.7%)	339 (38.5%)	131 (14.9%)	17 (50%)	0 (0%)	2 (5.9%)	0 (0%)	0 (0%)