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Sex Distribution and Sex Data Handling in Published Otolaryngology Research

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INTRODUCTION

Sex plays a significant role in disease burden and can influence response to treatment such as through pharmacokinetic alterations.1,2 However, it was not until the late 1980s that women were included in clinical trials. The United States Food and Drug Administration excluded premenopausal women from the early phases of most clinical studies until 1977.3 The US Public Health Service Task Force on Women’s Health Issues was established in 1983, and demonstrated that this ban on women significantly reduced the quality of information guiding the treatment of female patients.4,4 Subsequently, the NIH Revitalization Act of 1993 required the inclusion of women in clinical trials and established the Office of Research on Women’s Health to enforce this policy.4 The National Institutes of Health (NIH) currently require that all projects submitted for grant funding include plans for the inclusion of women and minorities.5

Internationally, Canada also established a guideline for the inclusion of women in clinical trials in 1997.6 However, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, which oversees the European Medicines Agency, has no specific policy regarding inclusion of women in clinical trials, though they specify that research populations should reflect overall demographics.7 Similarly, Australia has no policy governing sex inclusion in research.8

Although policies regarding the inclusion of women in clinical trials and research have been created, whether or not those policies have been followed or enforced must be determined by analysis of the research produced. Several fields, from basic and translational science to clinical research, have done analysis of published data for this exact purpose.9-12 A recent study demonstrated sex bias in the general surgery literature and called for improvements in national policy to address this disparity.13 As no similar assessment of sex in published data exists for the field of otolaryngology, the purpose of this study was to characterize the sex distribution and sex data handling in published otolaryngology research.

MATERIALS AND METHODS

Data were collected as previously described by Mansukhani et al.13 Selection of journals was based both on impact factor according to the Thomson-Reuters’ Journal Citation Reports
(JCR) and proportion of clinical studies. Head & Neck–Journal for the Sciences and Specialties of the Head and Neck, JAMA Otolaryngology–Head & Neck Surgery, Clinical Otolaryngology, The Laryngoscope, and Otolaryngology–Head & Neck Surgery were selected for analysis. All journals ranked in the top 10 of the 2016 JCR with an impact factor >2.2.

All original articles published from January 1, 2016 to December 31, 2016 as well as those published January 1, 2006 to December 31, 2006 were reviewed for inclusion in this study. Studies were excluded 1) if they were not original research publications or 2) if they did not contain human participants. Methodology and characteristics of studies examined are described in Figure 1. Data were collected manually by the first author. Institutional review board analysis was not required, as this study drew from previously published, deidentified publicly available data.

Variables abstracted included: journal of the publication, first author name, title of article, domestic or international study, single or multicenter study, total number of study participants, inclusion of specification of participant sex, number of male and female participants, and sex data handling. The latter variable was further stratified to assess for reporting of data by sex, any sort of analysis of data by sex (a category that included analysis done to show no difference in sex between two groups being compared or odds ratio between the two sexes), and discussion of sex-based results. The studies were subsequently categorized by subspecialty, including head and neck (H&N) cancer, infectious, laryngology, hearing, pediatric, reconstruction (including cosmetic), rhinology, noncancerous salivary gland pathology (salivary), sleep medicine, speech and swallow, thyroid, vestibular, and uncategorized for any remaining studies. H&N cancer was further subcategorized into salivary gland tumors (H&N salivary) and squamous cell cancers (SCC) (H&N SCC) for separate analysis.

The H&N cancer category included all studies from H&N salivary and H&N SCC as well as studies regarding unspecified tumor types.

Total number and percentages of male and female participants were reported. The proportion of male and female participants was calculated for each study by dividing the number of participants of each sex by the total number of participants. The average proportion for different categories was reported. The number of articles where outcomes were stratified according to sex, analyzed by sex, and discussed by sex were tallied separately and expressed as percentages of the total number of articles reviewed. χ² tests were used to compare the numbers of males, females, and unspecified sex participants in the studies presented in each journal, between domestic and international publications, between single-site and multicenter publications, and among studies published by the different fields. χ² tests were also used to compare the handling of sex data among the different studies in each journal, between domestic and international publications, between single-site and multicenter publications, and among studies published by the different fields. Lastly, t tests or analysis of variance (ANOVA) were conducted to compare the average sex proportions. Comparisons were made between domestic and international publications, between single-site and multicenter publications, between publications from 2006 and 2016, and among studies published by the different fields. Significance was assumed for P < .05. RStudio software (RStudio Inc., Boston, MA) was used for statistical analysis.

RESULTS

Total Sex Distribution of All Studies Included

A total of 1,593 articles were abstracted from all 2016 issues of Head & Neck–Journal for the Sciences and Specialties of the Head and Neck, JAMA Otolaryngology–Head & Neck Surgery, Clinical Otolaryngology, The Laryngoscope, and Otolaryngology–Head & Neck Surgery.
465 were excluded based on the aforementioned exclusion criteria (Fig. 1). Of the 1,128 studies included in the analysis, 88.5% specified the sex of participants, for a total of 3,605,636 (42.1%) men and 4,515,508 (52.8%) women (Fig. 2A). The remaining 11.5% of studies accounted for 429,006 (5.0%) participants with unspecified sex.

A total of 1,312 articles were abstracted from all 2006 issues of the same journals, and 418 articles were excluded (Fig. 1). Of the 894 papers included in the

![Graph A](image1.png)

![Graph B](image2.png)

![Graph C](image3.png)

![Graph D](image4.png)

![Graph E](image5.png)

Fig. 2. (A) Sex distribution of the total number of subjects across all included 2016 studies, categorized as male, female, and unspecified. (B) Sex distribution of total number of subjects across all included 2016 studies, compared by whether the research had been done on subjects in the United States (domestic) or elsewhere (international). Distributions were significantly different between domestic and international populations \((P < .001)\). (C) Sex distribution of total number of subjects across all included 2016 studies, compared by whether the subjects came from a single institution (single site) or multiple institutions (multicenter). Distributions were significantly different between single site and multicenter populations \((P < .001)\). (D) Sex distribution of total number of subjects across all included 2016 studies, compared by the journal in which the study was published. Distributions were significantly different between the different journals \((P < .001)\). (E) Sex distribution of total number of subjects across all included 2016 studies, compared by the subspecialty in which the research was conducted. Distributions were significantly different between all the subspecialties \((P < .001)\). H&N = head and neck; JAMA = Journal of the American Medical Association.
analysis, 97.2% specified the sex of participants, for a total of 318,255 (39.5%) men and 315,216 (39.1%) women. The remaining 2.8% of studies accounted for 172,220 (21.4%) participants with unspecified sex.

**Sex Distribution**

Sex distribution by total number of participants was different by origin of the study, number of institutions in study, journal in which the study was published, and subspecialty of the study. Studies from 2016 were categorized by whether they had originated from the United States (domestic) or another country (international), and the total sex distribution of each category was assessed (Fig. 2B). Of the 597 domestic studies, 38.1% of participants were male, 55.7% were female, and 6.2% were unspecified. Of the 531 international studies, 49.1% were male, 47.9% were female, and 3.0% were unspecified.

Studies from 2016 were also categorized by whether the research was conducted at a single institution or multiple institutions (Fig. 2C). Of the 922 single-site studies, 40.1% of participants were male, 33.4% were female, and 25.8% were unspecified. Of the 206 multicenter studies, 42.2% were male, 53.2% were female, and 4.6% were unspecified.

Total sex distributions of the 2016 studies from each journal were also assessed (Fig. 2D). The 95 studies included from Clinical Otolaryngology represented 60,639 participants, of which 31.9% were male, 22.6% were female, and 45.8% were unspecified. The 244 studies included from Head & Neck represented 158,362 participants, of which 68.6% were male, 29.1% were female, and 2.4% were unspecified. The 170 studies included from JAMA Otolaryngology represented 4,027,644 participants, of which 48.0% were male, 48.0% were female, and 4.0% were unspecified. The 380 studies included from The Laryngoscope represented 2,759,218 participants, of which 38.0% were male, 61.4% were female, and 0.6% were unspecified. Lastly, the 239 studies from Otolaryngology–Head & Neck Surgery represented 1,544,250 participants, of which 32.1% were male, 53.6% were female, and 14.3% were unspecified.

Lastly, sex distributions of the 2016 studies were compared by subspecialty (Fig. 2E). The 114 studies included in rhinology represented the greatest number of participants at 4,892,928, with 44.0% male, 54.8% female, and 1.2% unspecified. The majority of this number was due to two large national studies regarding rhinosinusitis. The 32 studies included in sleep medicine represented the fewest number of participants at 3,517, with 73.1% male, 22.5% female, and 4.4% unspecified. Sleep medicine, reconstruction, laryngology, H&N SCC, and H&N cancer had a predominance of men by total number of participants. On the other end, thyroid, speech and swallow, infectious, rhinology, and uncategorized had a predominance of women by total number of participants.

**Average Sex Proportion**

A different comparison, termed the average sex proportion (in contrast to the distribution of sex by total number of participants), was calculated by averaging the values of male and female proportions for each study. This calculation weighted each study the same and reduced the influence of large studies on the analysis.

The average proportion of male and female participants across all 2016 studies was 0.579 and 0.421, respectively (Fig. 3), in comparison to the sex distribution of total participants, which was 44.4% male and 55.6% female. International studies had a significantly higher average proportion of males in comparison to domestic studies (Fig. 3A), at 0.599 compared to 0.560, respectively (95% confidence interval [CI]: 0.07 to −0.01, \( P = .009 \)).

**Average Sex Proportions Across Subspecialties**

The average proportion of male and female participants for different subspecialties varied (Fig. 4) and were significantly different (\( P < .001 \)). Similar to the pattern demonstrated by distribution by sex, sleep medicine consistently had the highest average proportion of men, whereas thyroid medicine consistently had the lowest average. Other average proportions for both 2006 and 2016 are reported in Figure 4.

When comparing 2006 to 2016, H&N SCC was the only subspecialty that demonstrated a significant difference in average sex proportion, with an increase in the proportion of women from 0.210 in 2006 to 0.276 in 2016 (95% CI: 0.01 to 0.13, \( P < .05 \)) (Fig. 4). No significant differences were noted for the overall proportion or for any other subspecialty between 2006 and 2016.

**Handling of Sex Data**

Overall, 88.5% of studies from 2016 specified the sex of their participants, 20.8% reported outcomes by sex, 38.7% performed analysis on the sex data, and 15.2% discussed the results with reference to sex (Fig. 5). Comparison of single-site and multicenter studies revealed that multicenter studies were significantly more likely to report outcomes by sex, perform analysis with sex data, and discuss the results with reference to sex (Fig. 5B).

Although significantly fewer studies specified the sex of their participants in 2016 than in 2006, more studies analyzed sex-related data. In 2006, 97.2% of studies specified the sex of their participants, 18.8% reported outcomes by sex, 23.3% performed analysis on the sex data, and 16.0% discussed the results with reference to sex (Fig. 5C). In comparison to sex data handling from 2006, studies in 2016 were significantly less likely to specify the sex of their participants but significantly more likely perform analysis with sex data.

**Handling of Sex Data Across Subspecialties**

Certain subspecialties differed significantly in their handling of sex data in 2016 (Fig. 5C). Studies within H&N cancer were significantly more likely to perform analysis on sex data. A subset of this subspecialty, salivary tumors, was significantly more likely to report outcomes by sex, but significantly more likely to perform analysis on sex data. The other subset of this subspecialty, salivary tumors, was significantly more likely to discuss results with reference to sex. Studies within laryngology were significantly more likely to perform analysis on sex data. Studies within speech and swallow
Fig. 3. (A) Average proportion of male and female subjects among all 2016 studies, compared by whether the research had been done on subjects in the United States (domestic) or elsewhere (international). Proportions were significantly different between domestic and international studies (95% confidence interval [CI]: −0.07 to −0.01, $P = .009$). (B) Average proportion of male and female subjects among all studies, compared by whether the subjects came from a single institution (single site) or multiple institutions (multicenter). Distributions were not significantly different between single site and multicenter studies (95% CI: −0.04 to 0.02, $P = .599$). Error bars denote standard error.

Fig. 4. Average proportions of male and female subjects of each study, across all studies conducted in each subspecialty, separated by year, in descending order of 2016 average proportion of males. Error bars denote standard error. *Head and neck squamous cell carcinoma (H&N SCC) had a significant increase in the proportion of women from 2006 to 2016 (95% confidence interval: 0.01 to 0.13, $P < .05$).
Fig. 5. Percentage of 2016 studies that had specified the sex of their participants, reported the results of the study by sex, completed the analysis with the sex data, or discussed the results with reference to sex. (A) Percentages of 2016 studies by type of analysis conducted, compared by whether the research had been done on subjects in the United States (domestic) or elsewhere (international). Percentages were not significantly different between domestic and international studies ($P > .05$). (B) Percentages of 2016 studies by type of analysis conducted, compared by whether the subjects came from a single institution (single site) or multiple institutions (multicenter). Significant differences are marked by asterisks: single site (analyzed with $P < .001$, discussed with $P < .001$) and multicenter (outcomes reported with $P = .002$, analyzed with $P < .001$, discussed with $P < .001$). (C) Percentages of studies by type of analysis conducted, compared by year of study. Significant differences are marked by asterisks: sex specified with $P < .001$ and analyzed with $P < .001$. (D) Percentages of 2016 studies by type of analysis conducted, compared by the subspecialty in which the research was conducted, in order of descending proportion of studies with sex specified. Significant differences are marked by asterisks: head and neck (H&N) cancer (analyzed with $P < .001$), H&N squamous cell carcinoma (SCC) (outcomes reported with $P = .019$, analyzed with $P = .003$), laryngology (analyzed with $P = .032$), H&N salivary (discussed with $P = .003$), uncategorized (analyzed with $P = .011$), and speech and swallow (sex specified with $P = .032$, discussed with $P = .013$).
were significantly less likely to specify the sex of their participants, but more likely to discuss results with reference to sex. Lastly, uncategorized studies were significantly less likely to perform analysis on sex data. No other subspecialty handled their sex data in a manner significantly different from overall.

**DISCUSSION**

This is the first study in the field of otolaryngology to assess the sex distribution of participants and sex data handling across multiple journals, years, and subspecialties. We have chosen to separate the analyses from 2006 and 2016 in effort to elucidate underlying trends. Our focus is primarily on 2016 to present data that are most relevant to current-day research. Our results show that although there was a greater number of total female participants than male participants, the average sex proportion across all articles was higher for male participants. Whereas sex distribution was significantly different between various categories (Fig. 2), our study focused primarily on the average sex proportion given that it weighted each study the same. Analysis by average sex proportion circumvented the problem of having a few large-scale studies on the order of hundreds of thousands of participants overshadowing hundreds of studies that may have only had a few hundred participants each. This also avoided the problem that large sample sizes may result in magnification of minute differences to become statistically significant without corresponding clinical significance.

Given that our results also show that multicenter studies have a higher percentage of total female participants than single-site studies, this suggests that the majority of female participants were accounted for by multicenter studies, which were often epidemiological studies that drew from large national databases. Meanwhile, single-site studies, which were more often randomized controlled trials or prospective studies, had proportionally fewer total female participants (Fig. 2C). When articles were weighted the same in a comparison of average proportions, both single-site and multicenter studies had a greater proportion of male participants than female, suggesting that only a small number of multicenter studies might have been responsible for elevating the total count of female participants (Fig. 2E).

Studies originating from the United States were significantly more likely to include female participants than studies originating from other countries. This was evident in both the total number of participants (Fig. 2A) and in the average sex proportion (Fig. 3A). This is consistent with Mansukhani et al., who also showed that surgical studies originating from the United States included more female participants than studies originating elsewhere. It is possible that the early effects of specific sex-inclusion policy in the United States played a role in the significantly higher number and proportion of female participants.

Given that many disorders preferentially affect one sex, the variety in sex proportions seen across certain subspecialties are expected (Fig. 4). For example, H&N cancer affects patients in approximately a 3:1 male to female ratio, whereas thyroid cancer affects patients in approximately a 1:3 male to female ratio. These ratios are adequately reflected in our study. However, the strong predominance of male participants in laryngology and reconstruction is more surprising, as the patient population for these fields was not expected to skew toward a specific sex.

In comparison to Mansukhani et al., who showed that 82.7% of surgical studies reported the sex of their participants, our results showed that 88.5% of otolaryngology studies in 2016 reported the sex of their participants, though it represented a significant decrease in comparison to 2006. Moreover, a minority of 2016 studies actually accounted for sex in their results or discussion. H&N cancer (including SCC, but not salivary) had a significantly greater proportion of studies perform analysis on sex data in comparison to the other subspecialties (Fig. 5C). This could be due to researchers being conscious of the implicit sex predilection of the disease. However, over 60% of studies from 2016 did not perform any sort of analysis on their data with regard to sex, suggesting that for the majority of studies, sex was not considered important enough of a variable to warrant statistical consideration. On the other hand, this represented an improvement from 2006, where over 75% of studies did not perform any sort of analysis on their data with regard to sex. Nevertheless, even fewer studies reported their outcomes by sex or discussed the impact of sex on their results. It is both possible and likely that significant differences between the sexes among the many studies that failed to perform any kind of analysis by sex were missed.

The NIH mandated that as of January 2016, all investigators “account for the possible role of sex as a biological variable, beginning with the development of the research questions and study design and continuing through data analyses and reporting.” As this study falls into the period of time directly after implementation of this policy, it serves as an immediate baseline against which future meta-analyses can be compared. However, this NIH policy, along with previous policies regarding the inclusion of women and minorities, are enforced primarily at the research planning and grant application stage, without any stipulations regarding what is written in the publication submissions. Moreover, nearly half of the studies included in this study originated from outside of the United States, none of which fall under the purview of any NIH policies. Indeed, rather than rely on country-specific policies, it may be more advantageous to look for other forms of leadership, such as among journal editors and within the peer-review process, to encourage a more uniform and improved approach to handling sex data. Requirements that manuscript submissions include consideration of sex within the analysis may help elucidate and disseminate important information that could benefit clinical care for all patients.

Limitations of this study include that this was a limited sample of studies from only 2 years. Though we chose journals that had a high impact factor, they may not fully represent all of otolaryngology research, especially among subspecialties that have their own journals. Furthermore, we acknowledge that whereas this study has identified many statistically significant comparisons, the clinical significance of these comparisons is difficult to judge given that no similar study has been performed previously and because sex data handling continues to occur only in a minority of published studies. Moreover, we acknowledge that the categorization of subspecialties is subjective, as there was overlap between many of the subspecialties named, and certain articles could have been sorted into multiple subspecialties. Lastly, it is difficult to exactly
interpret the sex proportions of each subspecialty, given that most categories are comprised of multiple pathologies with a wide range of implicit sex predilections. In the future, studies could be sorted by specific disease to compare against known prevalence.

CONCLUSION

In otolaryngology research, there was a higher average proportion of male participants in comparison to female when studies were weighted equally. Studies originating in the United States included a greater number of female participants than those originating elsewhere, a possible result of explicit sex-inclusion policies governing research in the United States. Inclusion of women did not dramatically changed from 2006 to 2016, but analysis of sex data improved in 2016. Improvement of reporting, analysis, and discussion with regard to sex would benefit otolaryngology research and improve treatment for both sexes.

BIBLIOGRAPHY