



Reporting and analyses of sex/gender and race/ethnicity in randomized controlled trials of interventions published in the highest-ranking anesthesiology journals

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Aim: We assessed reporting of data on sex/gender and race/ethnicity in randomized controlled trials of interventions published in the highest-ranking anesthesiology journals from 2014 to 2017. **Methods:** We extracted data regarding terminology for sex/gender, proportion of participants according to the race/gender and race/ethnicity, and results shown for the race/gender and race/ethnicity. **Results:** Among the analyzed 732 trials, few stratified allocation of participants on the basis of sex/gender and race/ethnicity, few reported results for sex/gender or race/ethnicity and the outcomes reported may be influenced by one or both. **Conclusion:** In conclusion, outcomes of anesthesiology trials could be vulnerable to an important and avoidable source of bias; trialists need to pay more attention to sex and race/ethnicity when designing and reporting their studies.

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Importance of the role of sex and ethnicity in pathology, diagnosis, prevention and treatment of diseases has been increasingly emphasized. Analysis of Geller *et al.* conducted in trials from the fields of general internal medicine, oncology, cardiology, infectious disease, and obstetrics and gynecology, published in nine prominent medical journals in 2009 showed that median proportion of women in trials that included both men and women was 37% [1]. In 2016 such analysis of trials published in two prominent journals showed that the proportion of women was 41% [2]. Geller *et al.* showed that 75% of trials did not have any outcome analyses based on sex [1], while the 2016 study did not find a single trial that had prespecified analysis of differences by sex [2]. Similar lack of attention to race/ethnicity was found. Geller *et al.* also indicated that 21% of trials did not report race or ethnicity of their sample, and 64% did not do any analyses based on race/ethnicity [1].

In the field of pain, influence of sex on experimentally induced pain and pain sensitivity is still the subject of debate [3,4]. However, lack of attention to sex-related reporting in clinical trials about pain has been noted in recent literature. A recent systematic review about sex differences in a specific field found that not a single study published on the subject reported outcome data separately by sex. So systematic review authors contacted authors of 46 included studies and 17 studies provided data, indicating that differences could be found for certain conditions and outcomes [5]. The authors recommended that future studies need to examine whether mechanisms of treatment efficacy differ between sexes, and consider the impact of pretreatment sex differences on response to treatment [5]. Insufficient reporting of sex effects was also found for systematic reviews about chronic pain [6].

Previous synthesis of evidence has concluded that future studies need to explore whether mechanisms of treatment efficacy differ between sexes, and take into consideration impact of pretreatment sex differences on response to treatment [17].

Likewise, many studies reported that race/ethnicity is associated with important differences between patients when it comes to pain [7–9]. For this reason, race/ethnicity should be reported among the baseline characteristics of patients and, when feasible, outcomes should also be reported per race/ethnicity so that we can gain more insight into potential differences associated with such differences between participants. Meta-research (research-on-research) that evaluates planning, reporting and dissemination of research can help us identify negative patterns in the literature and opportunities for improving study design and reporting of future studies [10–13].

The aim of this study was to assess reporting of data on sex and race/ethnicity in RCTs of interventions published in the highest-ranking anesthesiology journals, including stratification methods, results and differences in efficacy outcomes. Rationale for this study is to provide empirical evidence that will help create suggestions for the improvement of future trials in terms of reporting and analyses regarding sex and race/ethnicity.

Methods

Study design

This was a primary methodological study (i.e., a research-on-research study that may also be described as meta-research) in which we analyzed descriptive characteristics of a sample of RCTs published in peer-reviewed journals. We conducted only analysis of published manuscripts; we did not include any participants or any personal patient data and therefore, the need for approval of the Institutional Review Board of the University of Split School of Medicine was waived.

Inclusion & exclusion criteria

We included RCTs of interventions that were published from January 2014 to December 2017 in the first-quartile journals indexed in the Journal Citation Reports (category Anesthesiology. We did not have determine *a priori* cutoff value for a Journal Impact Factor (JIF); we relied on information provided by the company Clarivate Analytics, who calculate JIF, and based on the list of journals that belong to each category (in this case, category ‘Anesthesiology’), they provide information about which journals belong to the first quartile in a category in a given year. Based on the 2017 *Journal Citation Reports JIF*, we included the following seven journals (in alphabetic order) *Anaesthesia*, *Anesthesia* and *Analgesia*, *Anesthesiology*, *Pain*, *British Journal of Anaesthesia*, *European Journal of Anaesthesiology*, *Regional Anesthesia* and *Pain Medicine*.

Search

We searched MEDLINE using advanced search feature with a journal name, filter for trials and filter for the chosen dates. We exported bibliographic records (titles and abstracts) of search results to EndNote X5 (Clarivate Analytics, PA, USA) reference management software. Two authors independently screened titles/abstracts and full texts if necessary against inclusion criteria. Any disagreements were resolved via discussion. Full texts of included trials were downloaded for data extraction.

Data extraction

We used Microsoft Excel (Microsoft Inc., WA, USA) to prepare data extraction sheets, which were piloted on ten first studies for consistency and clarity. We extracted the following data: name of the study, year of publication, journal name, terminology related to sex (sex, gender, male, female, men, nonbinary, transgender, women, availability of stratification based on sex and race/ethnicity in methods, number of men and women), stratified allocation of participants based on sex and race/ethnicity in methods, number of men and women enrolled, number of members of different race/ethnicity enrolled, prespecified sex-related or race/ethnicity related analyses in methods, presence of sex-related or race/ethnicity related analyses in results, type of analysis planned, type of analysis reported, numerical data about differences in efficacy of tested interventions related to sex and race/ethnicity and presence of information about sex-related or race/ethnicity results in discussion.

For the purpose of our analysis, we did not have prespecified definitions of sex/gender or race/ethnicity; we have extracted any information that we found in the included manuscripts related to sex/gender and race/ethnicity.

Data analysis

Sample size was estimated based on previous report, where 500 studies were considered sufficient for an outcome of percent of women in included studies [14]. Our preliminary analysis of number of trials published in the targeted journals indicated that 4-year period would be sufficient to reach this sample. We used MedCalc statistical software,

Table 1. Characteristics of trials included in analysis.

Trial characteristics	n (%)
Journal	
– <i>Anesthesia & Analgesia</i>	159 (22)
– <i>Pain</i>	122 (17)
– <i>Anesthesiology</i>	113 (15)
– <i>British Journal of Anaesthesia</i>	106 (14)
– <i>Anaesthesia</i>	87 (12)
– <i>European Journal of Anaesthesiology</i>	80 (11)
– <i>Regional Anaesthesia and Pain Medicine</i>	65 (9)
Most common nonsex specific indications [†]	
– Total knee arthroplasty	25 (3.4)
– Cardiac surgery	23 (3.1)
– Low back pain	11 (1.5)
– Osteoarthritis	6 (0.8)
– Neuropathic pain	5 (0.7)
– Shoulder surgery	4 (0.5)
Countries where the trial was conducted	
– USA	169 (23)
– Canada	52 (7.1)
– Denmark	49 (6.7)
– UK	38 (5.2)
– Republic of Korea	37 (5.1)
– China	37 (5.1)
– Germany	36 (4.9)
– France	36 (4.9)
– Australia	25 (3.4)
– Netherlands	25 (3.4)
– The other	228 (31)

[†] Trial authors used great variety of expressions for studied indications; these are the most common indicated-related expressions used by authors.

v 15.2.1 (MedCalc Software bvba, Ostend, Belgium) to conduct data analysis. We presented descriptive statistics data as frequencies and percentages.

Results

We analyzed 732 RCTs published during 4 years between January 2014 and December 2017. The majority of analyzed RCTs were published in the journal *Anesthesia & Analgesia* (Table 1). Most of the trials were conducted in the USA (23%), followed by Canada, Denmark, UK, Republic of Korea and China (Table 1). The trials addressed large variety of indications; the most common indications that were not sex-specific were procedures related to total knee arthroplasty, cardiac surgery and low back pain (Table 1).

In 70 (10%) RCTs, there were no information about either sex/gender or race/ethnicity of participants. There were 120 (17%) trials that included only men or only women. Among the 88 trials that included only women, 84 trials analyzed gynecological conditions, while four trials analyzed condition that affects both men and women (diseases of the thyroid, fibromyalgia and migraine).

Of the 32 trials that included only men, six trials analyzed male urological conditions. In the remaining 24 trials that did not cover male-specific conditions, eight trials quoted specific differences between women and men as a motive for including only men; one trial simply said they included only men to avoid sex differences without any further specifications, while the majority of those trials – 17 (71%) of 24 – did not report reason for including only men.

Terminology

When we analyzed sex versus gender terminology, about half of the manuscripts used word ‘sex’, 15% used the word ‘gender’ and 5% used both (Table 2).

We analyzed usage of words denoting women and men in trials including both sexes. Terminology used for men was found in 482 (66%) trials; the most commonly used term was male (Table 2). Terminology used for women was found in 493 (67%) trials: the most commonly used term was female (Table 2). Not a single trial provided or referenced a definition about sex or gender. We did not find any trials that used descriptors ‘non-binary’ or ‘transgender’ for their participants.

Table 2. Details of terminology used.	
Terminology and its location	n (%)
Sex vs gender terminology	
– Sex	344 (47)
– Gender	113 (15)
– Both sex and gender	35 (5)
– None of those words	240 (33)
Terminology used for men	482 (66)
– Male	383 (79) [†]
– Only letter M	51 (11) [†]
– Men	46 (10) [†]
– Both male and men	1 (0.2) [†]
Terminology used for women	493 (67)
– Female	400 (81) [‡]
– Women	46 (9) [‡]
– Only letter F	45 (9) [‡]
– Both female and women	1 (0.02) [‡]
[†] Percent of 482 (number of articles that used any term for men).	
[‡] Percent of 493 (number of articles that used any term for women).	

Reporting, planning & analyzing sex/gender

Sex/gender terms were mentioned in background/introduction section of 32 (4.3%) trials and in inclusion/exclusion criteria of 82 (11%) trials. Analyses of sex/gender were planned in methods in 66 (9%) of the analyzed trials. In 66 (9%) trials authors reported in results data for at least one analyses related to sex/gender (beyond baseline information about participants). There were 51 (7%) trials that mentioned sex/gender in the discussion section.

Reporting, planning & analyzing race/ethnicity

Race or ethnicity of participants was reported in background/introduction section of 5 (0.7%). In seven (1%) trials, the authors mentioned race/ethnicity in inclusion/exclusion criteria. There were 12 (1.6%) trials that planned any analyses related to race/ethnicity in methods. In seven (1%) trials, authors reported analyses about race/ethnicity in the results section (beyond baseline information about participants), whereas seven (1%) of trials mentioned anything related to race/ethnicity in their discussion section.

Proportion of women & men in trials that included both sexes

Among the 732 RCTs, there were 526 (72%) that included both men and women and reported number of participants according to sex. In those trials, on average, there were 49% (range: 1.4–98%) of women. There were 16 (3%) trials that had 100% matching of women and men, in other words, equal number of women and men included.

Proportion of race/ethnicity

There were 87 (12%) of trials that reported any information about proportion of participants according to race/ethnicity. Median percent of white participants in those 87 trials was 80% (range: 0–100%). In two trials, all participants were white and in 21 trials, information about race/ethnicity was partially reported; for example, authors would only give number of white participants, but no information for the other participants. In the remaining 64 trials, authors reported from two to six different groups of participants based on race/ethnicity. In one study, the authors only indicated that the majority of participants were born in Denmark.

Prevalence of significant differences in analyses based on sex/gender & race/ethnicity

Earlier we showed whether analyzed trials had reported that they planned analyses for sex/gender and race/ethnicity, and if they did plan them, what was the prevalence of them actually reporting them. Hereby, we are showing prevalence of significant differences between groups of participants based on sex/gender and race/ethnicity.

In 66 (9%) trials that reported results of outcomes for sex-based analyses in results, 31 (47%) described that there was a significant difference between women and men in at least one analyzed outcome. Supplementary Material 1 shows examples of results that explored study outcomes in the context of sex/gender.

Among seven trials that reported results based on race/ethnicity, one trial reported significant difference in at least one analyzed outcome for participants of different race/ethnicity. There were no trials that reported stratified allocation of participants according to the sex/gender or race/ethnicity. Supplementary Material 2 shows examples of results reported for analyses related to race/ethnicity.

Discussion

In this study we found that very few anesthesiology trials seek to stratify allocation of participants on the basis of sex/gender and race/ethnicity, and that it is feasible that the outcomes reported are influenced by one or both. This demographic imbalance at baseline therefore renders outcomes vulnerable to an important and avoidable source of bias.

Along with studies about proportion of women and men, and prespecified analyses by sex, in trials published in prominent journals [1,2]; in 2018, Prakash *et al.* reported that only 4% of trials had 100% sex matching, and concluded that sex bias is still present in current-day clinical trials [15]. Our findings were similar to findings of Prakash *et al.* [15]. Since half of the studies that reported sex-related analyses showed that there was significant difference between women and men in at least one outcome, it appears pertinent to plan for such analyses *a priori* when designing RCTs in the field of anesthesiology.

A study published in 2017 by Welch *et al.* found that 98% of the analyzed trials described the demographics of the participants, only 6% reported subgroup analysis based on sex/gender, and none of that trials reported any comprehensive analysis about sex or gender [16]. Trial authors used varied terminology; some trials used the term gender, while others used the term sex. However, not a single RCT provided or referenced definition of sex or gender. Likewise, none of the trials explained any intention to conduct or specify gender or sex analysis [16]. In our sample of 732 trials, we also did not find any provision or reference of a definition for sex or gender.

Sex and gender are not synonymous [17], and therefore, these terms should not be used interchangeably. Our analysis shows that some authors even use both terms in one manuscript, indicating lack of understanding of this difference.

In the field of pain research, influence of sex on experimentally induced pain and pain sensitivity is the subject of an ongoing debate [3,4]. However, it has been highlighted recently that there is insufficient attention on sex-related reporting in clinical trials about pain [5]. Due to these studies that imply that there are sex differences in the context of pain and anesthesiology, we decided to conduct this study in this particular field of research.

Insufficient reporting of sex effects was also found by Duan-Porter *et al.* in systematic reviews [6]; most reviews that reported sex effects used meta-regression analysis, whereas nine systematic reviews used subgroup analysis or individual-patient data meta-analysis [6].

Previous studies have also warned about lack of attention to race/ethnicity in trials [1] and that race/ethnicity was associated with important pain-related differences between participants [7–9]. Therefore, race/ethnicity should be reported as relevant information about the baseline characteristics of participants. Furthermore, attempts should be made to report outcomes based on race/ethnicity so that more insight can be gained into potential differences in the effect of interventions related to race/ethnicity.

When trials reported race/ethnicity of participants, 80% of participants were described as white or Caucasian, which could be due to lack of trialists' effort to recruit balanced sample, but also due to certain groups' unwillingness to participate in clinical trials [18].

There are several potential reasons why sex/gender and ethnicity/race are not considered in a large proportion of studies. This could be ascribed to oversight, lack of understanding, funding issues, conducting study in a country with less ethnic diversity and recruitment difficulties. Ethnicity could exert influence over the likelihood that individuals will give consent to participate in trials. Often times, it is probably simply lack of regard for these issues, as many analyzed trials did not even report demographics of their patients, let alone some analyses. Reporting demographics would have been simple, and for this reason, awareness about these important aspects of trial design and reporting should be increased among trialists.

A limitation of our study is that we did not aim to retrieve and analyze registered trial protocols, so we cannot make any conclusions about whether our included trials perhaps planned to do sex-specific analyses, but failed to report them subsequently. We only analyzed information available in manuscripts published in the target journals. Furthermore, in this study, we did not include all clinical trials, but only RCTs because they are considered the highest level of primary evidence in the hierarchy of medicine; therefore, these findings may not be generalizable to all types of clinical trials. Earlier analysis of sex/gender reporting in the field of anesthesiology included the first

issue of eight anesthesia journals published in 2017 and any type of study that included live women and men [14]. That study showed higher number of reporting by sex/gender compared with our study, which was focused on RCTs only. Our study shows that trials are doing worse in this respect, compared with any type of studies on humans [14].

The sample of included trials was not divided in any subgroups, which also might be considered a limitation, but our findings were consistent across the trials, in other words none of them had stratified allocation regarding sex or race/ethnicity, so we believe that the major findings of our trials are generalizable to various topics. The strength of our study is that we have analyzed a large sample of trials, and reached conclusions that may be very relevant to trialists for designing and reporting their trials.

In conclusion, we found that recent trials published in the highest-ranking anesthesiology journals devote suboptimal attention to issues of sex/gender and race/ethnicity, in terms of reporting baseline characteristics of participants, matching participants by sex, and conducting relevant analyses of outcomes. Higher awareness about importance of sex/gender and race/ethnicity reporting is needed among trialists in the field of anesthesiology. Furthermore, since half of the trials that did make sex-based analyses have reported significant differences between sexes for at least one outcome, it appears pertinent to make such analyses in all trials.

Summary points

- There is insufficient attention devoted to reporting about sex/gender and race/ethnicity in clinical trials.
- We have conducted analyses of terminology and analyses related to sex/gender and race/ethnicity in 732 randomized controlled trials from the field of anesthesiology.
- None of the trials defined sex/gender or race/ethnicity.
- Few trials reported information about sex/gender or race/ethnicity of participants.
- Trials used both expressions sex and gender even though they are not synonymous.
- Few trials planned statistical analyses based on sex or race/ethnicity.
- Trials that did make such analyses have found relevant differences in outcomes related to sex or race/ethnicity.
- Future trials should plan and report adequate information and analyses regarding sex and race/ethnicity because those factors may influence clinical outcomes.

Author contributions

L Puljak focused on study design. D Begic, C Janda-Martinac, M Vrdoljak and L Puljak dedicated to data collection and analysis, performed critical revision of the manuscript, approved final version of the manuscript and agreed to be accountable for the work. L Puljak contributed in writing first draft of the manuscript.

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Data sharing statement

The study did not include clinical trial, or secondary analysis of clinical trial data. All data collected and analyzed within this study are available from the corresponding author on request.

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