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Uneven global and racial representation in major orthopaedic clinical trials: Trends over a decade

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ABSTRACT

Background: The presence of geographic and demographic disparities in randomized controlled trials (RCTs) may affect the external validity of trials. While some studies have addressed racial or ethnic disparities, they have been limited to a certain region, and there is limited information about the global representation in orthopaedic research.

Methods: RCTs published in major medical and orthopaedic journals from 2010 to 2019 were identified. After screening 6961 articles, 1769 trials enrolling 323,506 patients were included. The details of individual trials such as the country of origin, the proportion of women, and the proportion of different racial groups were recorded. Factors associated with reporting and representation of specific demographic groups, and annual changes were assessed.

Results: Majority of the trials were from were from United States (US) (N = 380, 21.5%). US (30.7%, N = 99,356), United Kingdom (15.7%, N = 50,691) and Canada (8.3%, N = 26,890) accounted for majority of the enrolled patients. 59.1% of the patients were women. Among US trials reporting race, 81.2% were White, and 9.9% were African American. There was no significant variation in the global distribution ($p = 0.056$), percentage of women ($p = 0.811$), or percentage of Whites ($p = 0.389$) over the years.

Conclusion: The top three countries contributed to about 55% of the enrolled patients, whereas they contributed to only 6% of the world population. Overall, women appeared to be adequately represented in the trials, while racial minorities were underrepresented. There has not been any considerable improvement in the representation of developing regions or minorities over the last decade.

1. Introduction

Randomized clinical trials (RCT) are the pillars of evidence-based medicine, and provide the highest quality of evidence. Although only a few patients participate in the published clinical trials, the results of these trials are used to guide treatment of a diverse set of patients across the world. The presence of geographic and demographic disparities in clinical trials may affect the external validity of trials limiting their application to patient groups poorly represented in the clinical trials.[1] Racial and ethnic differences in trials have been reported in literature with respect to different specialities including orthopaedics, with reporting of race/ethnicity in clinical trials being low, and minorities being underrepresented.[2] However, previous studies addressing demographic disparities have largely focussed on addressing the racial or ethnic disparity within a country, and there is limited information about the global representation in orthopaedic research.

To improve the representation of different patient groups, demographic reporting is being encouraged by various research bodies and journals.[3–5] However, limited attention has been paid to global representation of trials. Demographic differences in the severity of illness, treatment utilization and treatment outcomes are well documented.[6–9] For example, in a systematic review by Nwachukwu et al.,[8] minorities were found to have higher risk of complications following total hip/knee arthroplasty. Therefore, trials on arthroplasty may overestimate the outcomes of an intervention if the minorities are underrepresented in the trials.[8] In

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addition to the demographic differences between countries, variations in health systems, health utilizations and orthopaedic practices exist globally. Understanding the global distribution of the studies provide valuable information about the actual diversity in orthopaedic research, and provide opportunities to improve global partnerships. In addition to the global differences, racial and gender diversity is important for external validity of clinical trials, and should be addressed.

Therefore, we conducted a review of all the orthopaedic RCTs published in major journals over the last decade to: 1) assess the global distribution of trials; 2) evaluate the reporting and representation of gender; and 3) evaluate the reporting and representation of racial groups.

2. Methods

This was a systematic review in adherence with the AMSTAR (Assessment of Multiple Systematic Reviews) and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines of all the published RCTS from January 1, 2010 to December 31, 2019 in orthopaedic surgery in three major medical journals and ten most cited orthopaedic journals (based on 2019 impact factor provided by Journal Citation Reports).[10–12] A systematic search of the PubMed online database was conducted to identify RCTS in the following journals using the journal title and publication type headers- The New England journal of medicine (NEJM), Lancet, JAMA, The American journal of sports medicine, The Journal of bone and joint surgery-American volume, Osteoarthritis and cartilage, Arthroscopy: the journal of arthroscopic & related surgery, Clinical orthopaedics and related research, Acta orthopaedic, Knee surgery, sports traumatology, arthroscopy, The Journal of arthroplasty, The spine journal, Journal of bone and joint surgery-British volume (now called as the bone & joint journal). As all these journals were indexed in PubMed, we did not search any other databases. Articles were screened independently by two reviewers to finally include 1769 trials in this study (Fig. 1). Any disagreement was resolved with the consensus of a third reviewer. When an RCT on the same set of patients was published multiple times (for example – 2 years follow up results and 5 years follow up results), the earlier article was included.

For each trial, the country of origin of the study was recorded. This was defined as the place where the study was conducted. For multicentric studies involving the multiple countries, the country with the maximum number of patients was considered to be the origin. Although sex and gender have different definitions with respect to research, they are often used interchangeably in most studies.[13] In the present study, we did not make a distinction between the two, and recorded gender as the number of men and women in each study. Since the reporting of race is heterogenous across countries, and there is no consensus with regards to reporting of race in various countries, we analysed the racial representation for only those trials originating from United States.[14] For racial and ethnicity reporting, we recorded data in accordance with the US Food and Drug Administration's reporting recommendations.[10] The presence or absence of any funding for the study, and the type of funding (public or private sector) was recorded. Impact factor of the journal was obtained from Journal Citation reports based on the 2019 rankings. The journals were grouped into low (<3.5), moderate (3.5–4.5), and high (>4.5) to have roughly equal distribution of trials.

Categorical variables were analysed using a Chi-squared or Fisher Exact test. Linear regression was used to assess the yearly change in gender and racial representation, as well as to assess the factors associated with increased representation of women or white race. Logistic regression was used to assess the factors associated with gender and racial reporting. Multivariate regression was used to identify the independent factors associated with increased representation of women/white race. Trials focusing on gender specific pathologies and including only one gender were not included in the regression analysis for gender representation. Only the variables significant in the univariate analysis were included for the multivariate analysis. The results of logistic regression were reported using odds ratio (OR) while that of linear regression was reported with beta coefficient. 95% confidence intervals (CI) were calculated. US and world population were obtained from US census and United Nations population data for comparison of representation of various groups in trials with the expected distribution.[15,16] A p-value of less than 0.05 was taken as the threshold for statistical significance. All analyses were performed using R software (version 3.1.3, Vienna, Austria).[17]

3. Results

Out of the 1769 trails, 380 (21.5%) were from US, 155 (8.8%) from South Korea and 128 (7.2%) from United Kingdom (UK). The country wise distribution of trials is given in Fig. 2. There was a total of 323,506 patients enrolled in these trials with the majority from United states (30.7%, N = 99,356), followed by UK (15.7%, N = 50,691) and Canada (8.3%, N = 26,890). The global distribution of cumulative number of patients is given in Fig. 3. 53 (3.0%) trials included patients more than one country. The characteristics of trials based on the region are given in Table 1. There were N = 128,864 (39.8%) patients from Europe, N = 126,246 (39.0%) from North America, N = 46,072 (14.2%) from Asia, and N = 22324 (6.9%) from other regions. There was no significant variation in the global distribution with year (p = 0.056) (Fig. 4). 62.1% (N = 1099) trials were unfunded, while 16.7% (N = 295) were funded by public sector, and 21.2% (N = 375) by private sector. Trails from Asia (83.1%) were more likely to be unfunded than those from Europe (58.6%) or America (50.8%) (p < 0.001). Majority of trials involved lower extremity (N = 1359), and arthroplasty (N = 872) was the most commonly published specialty. Trials from Asia (22.0%) were less likely to be published in high impact journals than those from Europe (33.6%) or America (43.4%) (p < 0.001). The average number of patients per trial was 182 (range, 8–12495). 23.3% (N = 413) trials had less than 50 patients, 36.5% (N = 646) had patients between 50 and 100, and 40.1% (N = 710) had over 100 patients. Trials from North America were more likely to have a larger sample size (p < 0.001).

Gender was reported in 94.6% (N = 1673) trials. There was a significant increase in reporting of gender from 2010 to 2019 (p = 0.002). There was no significant difference in reporting between the regions, funding, anatomical region, specialty, type of trial, or journal impact factor (Table 2). Increasing sample size was associated with increased likelihood of gender reporting (Table 2). Among the trials in which gender was reported, 59.1% (N = 184,698/312,364) were women participants. There was no annual change in the percentage of women participants (p = 0.811) (Fig. 5). 69 trials included patients of only one gender. Trials from Asia, trials on lower extremity, arthroplasty trials, trials in moderate impact factor journals, and trials with larger sample size were associated with increased percentage of women, while sports and trauma trials were associated with decreased percentage of women (Table 2). Based on specialty, women represented 67.3% (N = 31098/46190) of the general trials, 60.1% (N = 76621/127414) of the arthroplasty trials, 54.0% (N = 16970/31434) of the spine trials, 36.4% (N = 15684/43047) of the sports trials, and 69.0% (N = 44325/64279) of the trauma trials. On multivariate analysis, Asian origin (Coefficient = 8.91 [6.69–11.14], p < 0.001), upper extremity (Coefficient = 9.17 [2.70–15.65], p = 0.006), arthroplasty (Coefficient = 3.63

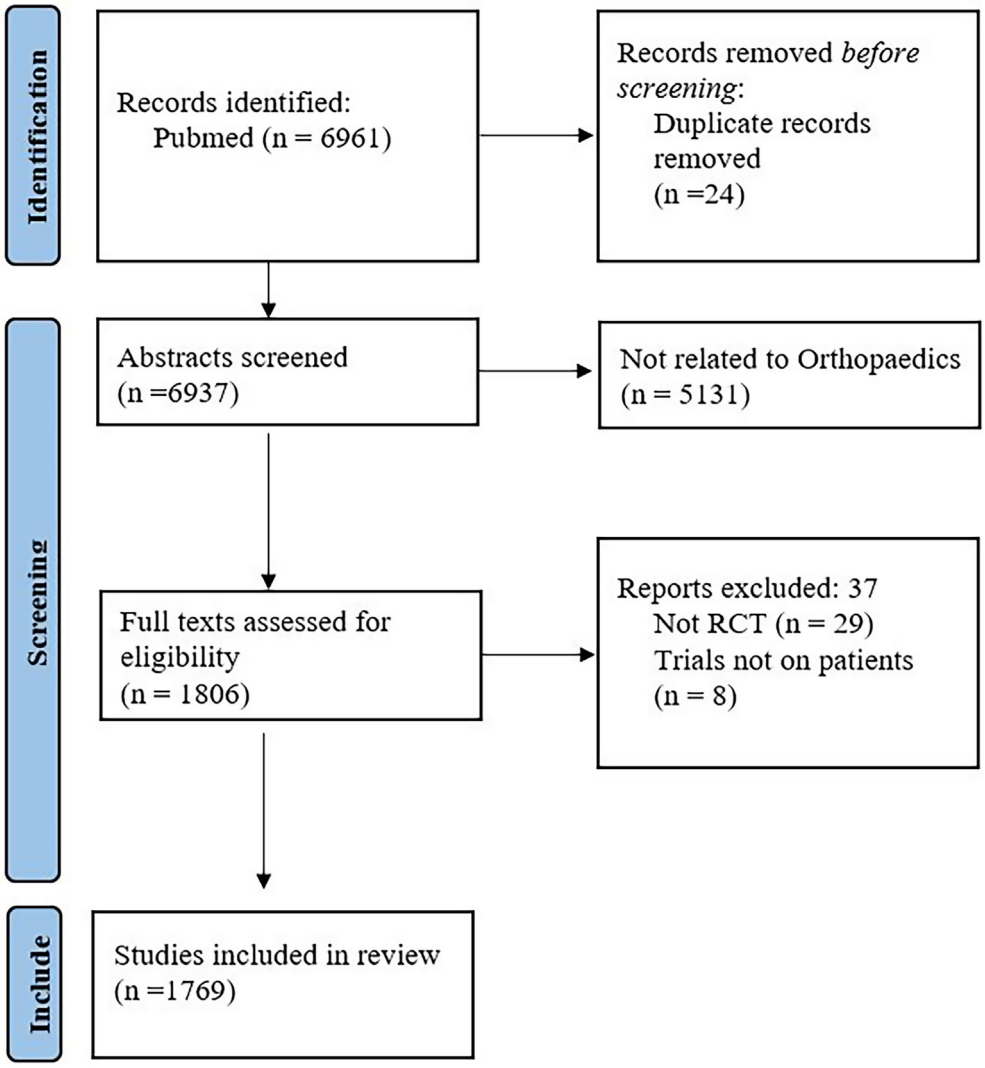

Fig. 1. PRISMA flowchart showing the selection of studies.

[0.23−7.03], p = 0.036) were associated with increased women representation, while sports (Coefficient = −19.07 [−22.59 to −15.54], p < 0.001) and trauma (Coefficient = −8.47 [−12.46 to −4.47], p < 0.001) were associated with decreased women representation.

Overall, race was reported in 116 (6.6%) trials. Among the 380 trials from United States, race was reported in 79 (20.8%) trials while in the 1389 non-US trials it was reported in 37 (2.7%) trials (p < 0.001). Among the US trials reporting at least one racial subgroup, 75.8% (N = 36267/47866) of the patients were White. Among the trials reporting at least two racial subgroups, 81.2% (26103/32148) were White, and 9.9% (3192/32148) were African American (Fig. 6). One trial included only African American patients. Ethnicity was reported in 27 (7.1%) of the US trials with Hispanics contributing to 7.8% (1010/12892) of the patients. The reporting of race in US trials improved from 16.7% in 2010 to 33.9% in 2019 (p = 0.046). Presence of funding and larger sample size were associated with increased reporting, while arthroplasty, trauma and sports trials, and surgical trials were associated with decreased reporting of race (Table 3). The prevalence of whites was lower in sports trials (p = 0.022). There was no difference with respect to representation of Whites based on year, funding, anatomical region, journal impact factor, type of trial, and sample size (Table 3).

4. Discussion

The demographic makeup of clinical trials should ideally closely mirror that of the actual diseased population. Underrepresentation of one or more population subsets in the published trials can result in the research being less generalizable. We reviewed 1769 RCTS enrolling 323,506 patients published in major journals, and found that majority of the orthopaedic research was represented by a few countries and this global disparity has not improved over the last decade. Gender and racial reporting improved over the years although racial reporting was still low. Overall, women (more than half of the patients were women) appeared to be adequately represented in the trials published in major journals, while racial minorities were underrepresented.[16]

Majority of the enrolled patients were from US, UK or Canada which contributed to about 55% of the patients, whereas these countries contributed to only 6% of the world population.[15] When origin was analysed by geographic regions, the majority of the trials were from Europe (40%) and North America (39%) while these regions contributed to only 10% and 5% of the world population.[15,18] This disparity in the origin of trials did not improve over the last decade. Lack of funding and language barrier might be a possible explanation for this disparity. Man et al.[18] reviews articles

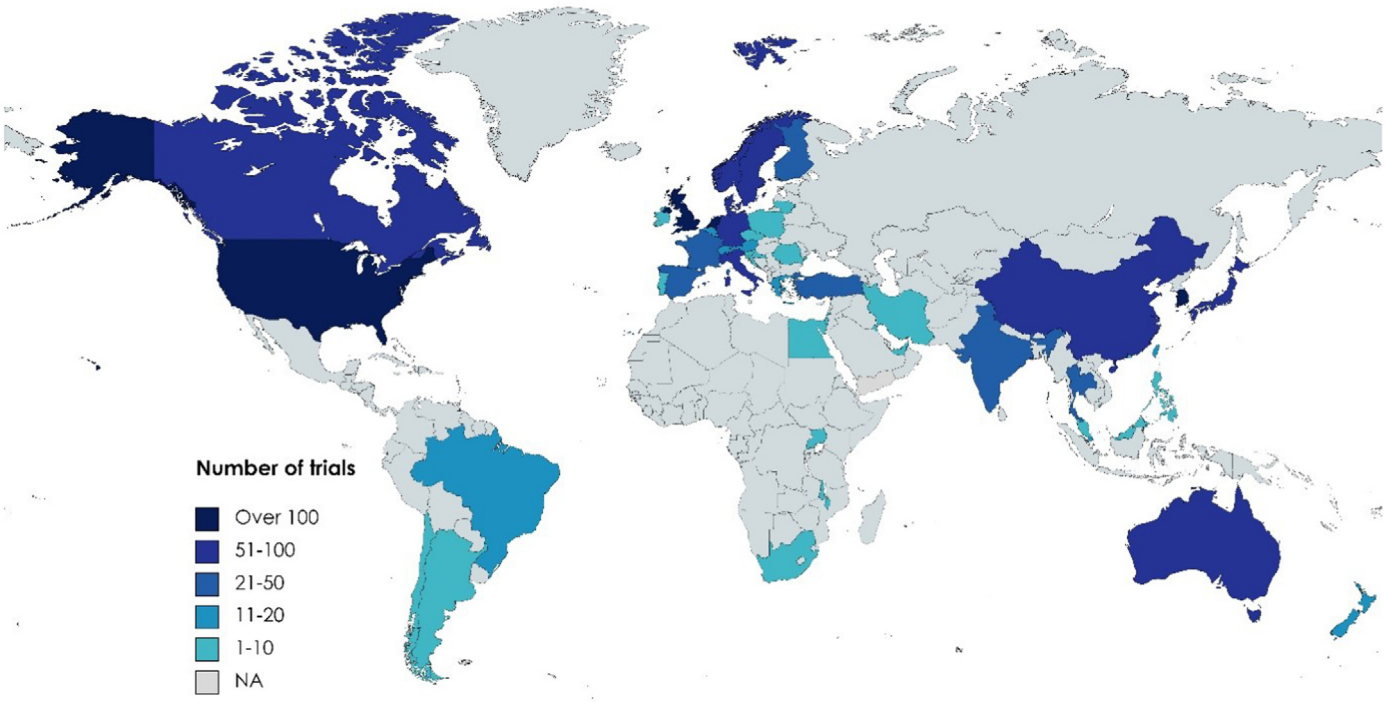

Fig. 2. Worldwide distribution of number of trials in orthopaedic surgery.

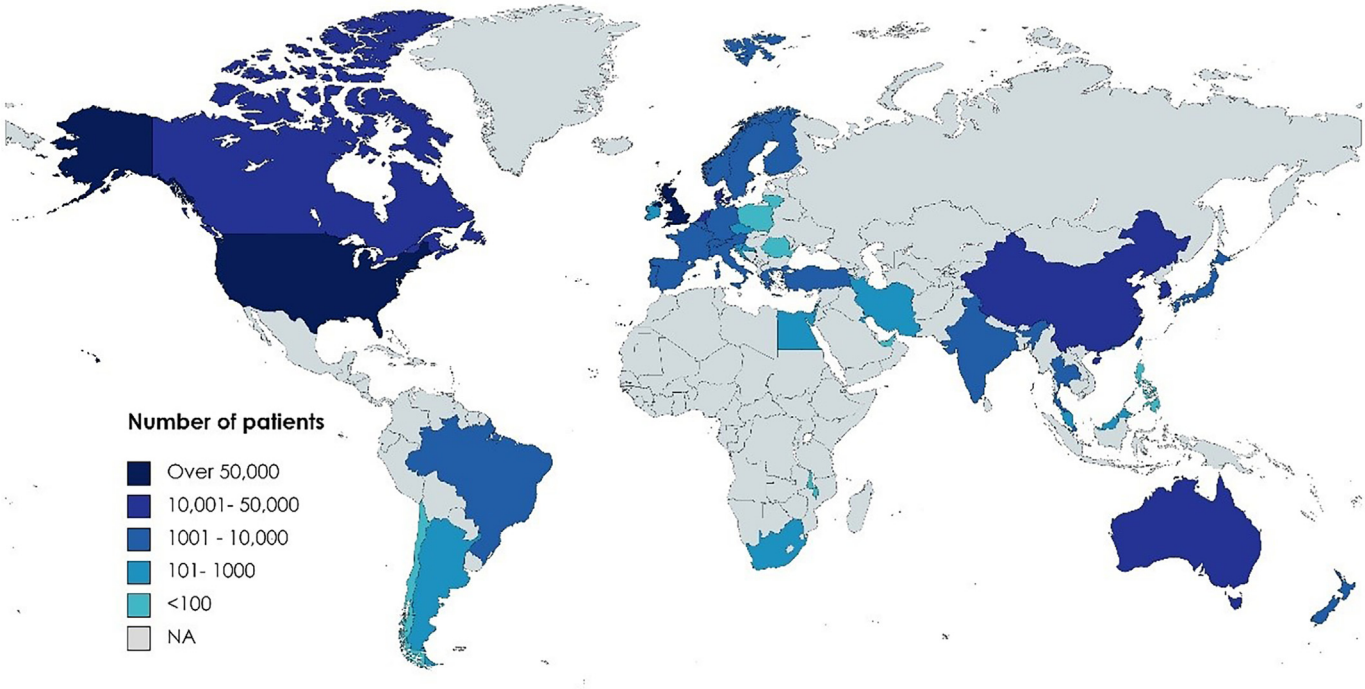

Fig. 3. Worldwide distribution of cumulative number of patients enrolled in orthopaedic trials.

appearing in the five highest ranked general medical journals between 1997 and 2001, and found that research spending and English proficiency were strongly associated with publication output of countries. The three countries in this study, which contributed to the majority of the enrolled patients, have English as the primary language which might have contributed to an ease in publication in the major journals. Yeung et al.[19] had reported disparity in the global distribution of hip fracture trials with the majority of the trials originating from Scandinavia and UK. Although the present study did not analyse pathologies separately disparity in global representation was found to be more pronounced for certain specialities like trauma.

Gender was reported in the vast majority of the studies (above 95%). Overall, majority of the enrolled patients were women.

Table 1
Study characteristics based on the region of origin of the study.

Variable	Europe (N = 742)	North America (N = 465)	Asia (N = 437)	Others (N = 125)	P-value
Year					0.052
2010	69 (9.3%)	34 (7.3%)	17 (3.9%)	6 (4.8%)	
2011	72 (9.7%)	33 (7.1%)	39 (8.9%)	13 (10.4%)	
2012	52 (7%)	40 (8.6%)	44 (10.1%)	12 (9.6%)	
2013	79 (10.6%)	40 (8.6%)	60 (13.7%)	10 (8%)	
2014	75 (10.1%)	53 (11.4%)	46 (10.5%)	14 (11.2%)	
2015	71 (9.6%)	49 (10.5%)	50 (11.4%)	10 (8%)	
2016	74 (10%)	42 (9%)	46 (10.5%)	13 (10.4%)	
2017	77 (10.4%)	46 (9.9%)	51 (11.7%)	20 (16%)	
2018	82 (11.1%)	65 (14%)	38 (8.7%)	16 (12.8%)	
2019	91 (12.3%)	63 (13.5%)	46 (10.5%)	11 (8.8%)	
Funding					<0.001
None	435 (58.6%)	236 (50.8%)	363 (83.1%)	65 (52%)	
Public	143 (19.3%)	82 (17.6%)	40 (9.2%)	30 (24%)	
Private	164 (22.1%)	147 (31.6%)	34 (7.8%)	30 (24%)	
Anatomical region					<0.001
Upper	112 (15.1%)	47 (10.1%)	66 (15.1%)	18 (14.4%)	
Lower	572 (77.1%)	350 (75.3%)	339 (77.6%)	98 (78.4%)	
Spine	45 (6.1%)	46 (9.9%)	25 (5.7%)	4 (3.2%)	
Others/Mixed	13 (1.8%)	22 (4.7%)	7 (1.6%)	5 (4%)	
Specialty					<0.001
General	71 (9.6%)	46 (9.9%)	29 (6.6%)	13 (10.4%)	
Arthroplasty	340 (45.8%)	255 (54.8%)	218 (49.9%)	59 (47.2%)	
Spine	41 (5.5%)	45 (9.7%)	22 (5%)	4 (3.2%)	
Sports	193 (26%)	69 (14.8%)	136 (31.1%)	31 (24.8%)	
Trauma	97 (13.1%)	50 (10.8%)	32 (7.3%)	18 (14.4%)	
Type of trial					<0.001
Medical	322 (43.4%)	284 (61.1%)	195 (44.6%)	64 (51.2%)	
Surgical	420 (56.6%)	181 (38.9%)	242 (55.4%)	61 (48.8%)	
Journal Impact factor					<0.001
Low	255 (34.4%)	36 (7.7%)	115 (26.3%)	13 (10.4%)	
Moderate	238 (32.1%)	227 (48.8%)	226 (51.7%)	48 (38.4%)	
High	249 (33.6%)	202 (43.4%)	96 (22%)	64 (51.2%)	
***Sample* size**					<0.001
<50	180 (24.3%)	97 (20.9%)	94 (21.5%)	42 (33.6%)	
50–100	277 (37.3%)	137 (29.5%)	196 (44.9%)	36 (28.8%)	
>100	285 (38.4%)	231 (49.7%)	147 (33.6%)	47 (37.6%)	

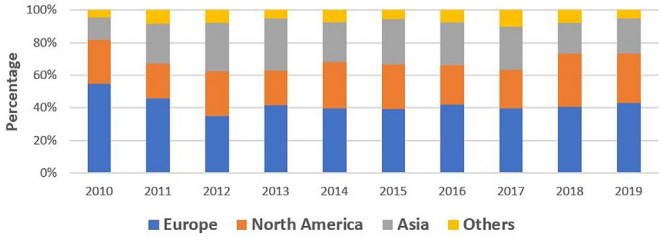

Fig. 4. Trends in global representation over the years.

Previous studies have reported higher rates of musculoskeletal problems in women which might explain the overall higher prevalence of women in the orthopaedic trials. As incidence of many pathologies are affected by gender, representation of gender as a whole may not be very helpful in evaluating any disparity.[20,21] However, we found that 60% of the patients in arthroplasty trials were women which was similar to the prevalence of women reported in various arthroplasty registries.[15,22] Similarly, the prevalence of women in spine trials closely resembles the prevalence reported in different spine cohort or registry based studies.[23,24] The lower prevalence of women in sports related trials might be due to the lower participation of women in sports and lower prevalence of sports related injuries in them. In an insurance database related study of over 80,000 sports injuries, only 25% of the injuries were reported in women.[23] In another study based on the NSQIP database, about 45% of the knee and shoulder arthr0scopy procedures were done in women.[25] Our findings are similar to other studies which failed to demonstrate any gender disparity in trials published in major journals.[26,27]

Racial reporting remained low especially in studies originating outside the US. In the present study, the overall reporting was about 7% which was similar to that reported by Paul et al.[28] who analysed 482 orthopaedic RCTS and found racial reporting of only 7%. The higher reporting of race in US trials was also shown by Sheikh et al.[14] The higher reporting in US trials is likely due to the stricter legislations in US such as the National Institutes of Health Revitalization Act 1993 which aims to improve minority representation.[5] As racial diversity in most countries is increasing, research bodies and journals should encourage trials from all countries to include racial/ethnic data. Moreover, there is also a need for uniform reporting of race/ethnic groups across studies. Although the reporting remained lower than desired, the racial reporting in US trials increased substantially over the past decade. Among the US trials that reported racial data, the representation of African American and Hispanics were lower than would be expected on the basis of census demographics (13% and 19% of US population is African American and Hispanics respectively, compared to 10% and 8% of the enrolled patients). Interestingly, the percentage of Whites were lower in studies reporting only one subgroup (76%) compared to those reporting at least two subgroups (81%). Although the reasons for this disparity is unknown, the overall White percentage in the present study (studies with at least one group reported) was similar to that reported by Loree at al.[29] in the FDA trials (76%) and closely resembles the US census data (76%).[16] The underrepresentation of minorities have been previously reported in orthopaedic trials and trials in other specialities.[2] Except for sports trial, none of

Table 2
Factors associated with reporting and representation of gender.

Variable	Reporting of Gender		Percentage of women	
	Odds ratio (95% CI)	P-value	Coefficient (95% CI)	P-value
Year	1.13(1.05–1.22)	0.002	0.04(-0.30–0.39)	0.811
Region of origin				
Europe	Ref		Ref	
North America	0.68 (0.43–1.09)	0.111	1.58 (−0.81–3.97)	0.195
Asia	1.81 (0.95–3.43)	0.069	8.24 (5.82–10.67)	<0.001
Others	0.72 (0.34–1.52)	0.381	−1.62 (−5.54–2.29)	0.415
Funding				
None	Ref		Ref	
Public	1.99 (0.98–4.06)	0.056	−1.15 (−3.82–1.52)	0.396
Private	1.01(0.61–1.66)	0.973	−0.97(-3.42–1.47)	0.433
Anatomical region				
General	Ref		Ref	
Upper extremity	0.68 (0.15–3.06)	0.611	1.99 (−5.07–9.06)	0.580
Lower extremity	0.79 (0.19–3.34)	0.753	7.37 (0.72–14.02)	0.030
Spine	0.72 (0.14–3.59)	0.686	7.54 (0.00–15.08)	0.049
Specialty				
General	Ref			
Arthroplasty	0.53 (0.21–1.35)	0.188	3.52 (0.29–6.75)	0.033
Spine	0.49 (0.15–1.58)	0.230	−1.61 (−6.21–3.00)	0.494
Sports	0.60 (0.22–1.61)	0.312	−16.91 (−20.40–13.43)	<0.001
Trauma	0.50 (0.17–1.45)	0.203	−8.06 (−12.06–−4.07)	<0.001
Type of trial				
Medical	Ref		Ref	
Surgical	1.09 (0.73–1.65)	0.666	−1.81 (−3.75–0.14)	0.069
Journal impact factor				
Low	Ref		Ref	
Moderate	1.68 (0.98–2.89)	0.057	2.83 (0.36–5.32)	0.025
High	0.98 (0.59–1.63)	0.948	−2.46 (−5.07–0.15)	0.064
Sample size				
<50	Ref		Ref	
50–100	1.66 (1.01–2.76)	0.047	2.49 (−0.12–5.11)	0.062
>100	1.90 (1.15–3.16)	0.013	4.15 (1.58–6.72)	0.002

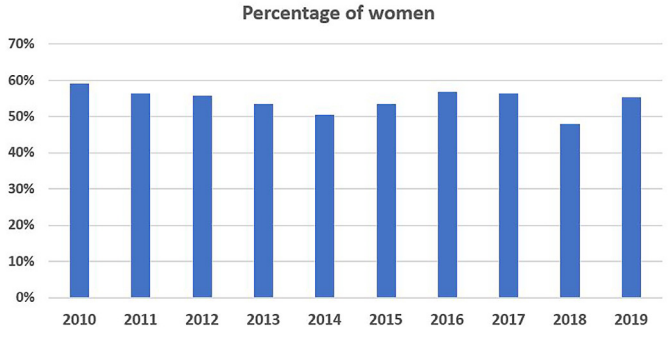

Fig. 5. Percentage of women among enrolled patients over the years.

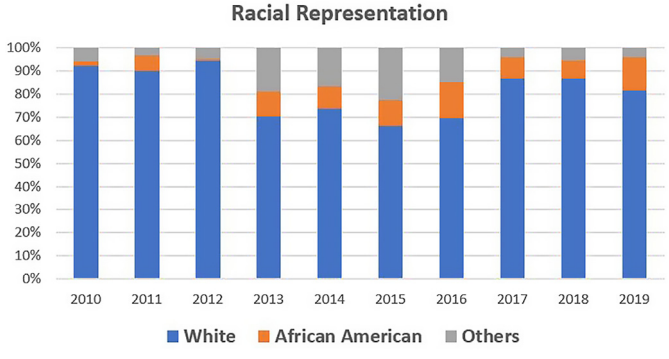

Fig. 6. Representation of racial groups in trials in United States over the years.

the factors assessed in this study were associated with racial disparity. The higher representation of minorities in sports trials may be related to increased representation of African American in sports.[30]

There are a number of limitations for this study. Although we considered the country with the maximum number of enrolled patients as the origin of the study, many large multicentric trials can have substantial contributions from different countries. However, only 3% of the studies were multinational and therefore it is unlikely to have affected the results of our study. In this study, the analysis was performed using the reported demographic details in the publication (full text article or supplementary material). It is possible that some studies might have analysed demographic data, but did not report it. We studied the overall gender representation among the orthopaedic trials. But many diseases are more common in either of the gender, and subgroup analyses based on individual diseases were not performed. Nevertheless, we compared the representation among the difference specialty groups which can be assumed to be reliable indicators of the underlying pathologies. With respect to racial representation, we only included studies originating in the United States. While every country is expected to have a racially heterogenous group, the reporting across countries is heterogenous with possibly overlapping definitions, making it difficult to have a combined analysis. Nevertheless, the diversity of trails based on the country of origin provides an indirect estimation of the racial representation of the global population in the orthopaedic literature. In this study, only RCTs published in major journals were included and a number of important RCTs which might have been published in other journals were not reviewed. Similarly, there are a number of journals in languages other than English which contribute significantly to the scientific literature. It is

Table 3
Factors associated with reporting and representation of race for those trials originating from United States.

Variable	Reporting of race		Percentage of white	
	Odds ratio (95% CI)	P-value	Coefficient (95% CI)	P-value
Year	1.09 (1.00–1.20)	0.046	−0.62 (−2.04–0.80)	0.389
Funding				
None	Ref			
Public	4.16 (2.14–8.09)	<0.001	0.12 (−10.46–10.71)	0.982
Private	1.87 (1.04–3.35)	0.037	−1.25 (−11.23–8.72)	0.803
Anatomical region				
General	Ref			
Upper	0.14 (0.03–0.65)	0.012	0.69 (−24.97–26.34)	0.957
Lower	0.35(0.13–0.95)	0.039	7.84(-7.12–22.79)	0.300
Spine	1.05 (0.34–3.27)	0.936	8.92(-7.92–25.77)	0.295
Specialty				
General	Ref			
Arthroplasty	0.24(0.12–0.49)	<0.001	−0.94 (−11.41–9.52)	0.858
Spine	0.88 (0.37–2.11)	0.773	−0.25(12.58–12.08)	0.962
Sports	0.07 (0.02–0.26)	<0.001	−23.48 (−43.47–−3.49)	0.022
Trauma	0.32 (0.11–0.88)	0.027	−5.09 (−21.15–10.97)	0.530
Type of trial				
Medical	Ref		Ref	
Surgical	0.14 (0.06–0.32)	<0.001	−9.95(-23.59–3.69)	0.150
Journal impact factor				
Low	Ref		Ref	
Moderate	0.51 (0.19–1.40)	0.191	−5.52 (−22.58–11.53)	0.521
High	1.52 (0.58–3.96)	0.397	−0.54(-16.53–15.43)	0.946
Sample size				
<50	Ref		Ref	
50–100	0.67 (0.23–1.94)	0.469	0.74 (−18.57–20.06)	0.939
>100	4.58 (2.08–10.08)	<0.001	1.25(-12.74–15.25)	0.859

possible that the demographic makeup found in the present study would have been different if articles from other journals were also included. However, the purpose of the study was to review only the trials published in major journals as these journals are the most widely followed globally.

In summary, there was huge disparity in the representation of global population in major orthopaedic trails. There was no significant improvement with respect of global representation over the last decade. Lack of funding in underdeveloped countries might have resulted in smaller and low impact trials from these countries, leading to their underrepresentation in major journals. Gender reporting has significantly improved over the last decade although the gender representation remained unchanged and did not show any evidence of disparity. Racial reporting was low though there has been improvement in the reporting among US trials over the last decade. There was underrepresentation of minorities in trials which did not improve over the last decade. Further research is required to understand the reasons for this wide global disparity in orthopaedic trials. Increasing research funding, providing language services, and improving data collection measures may help in encouraging RCTs in countries or regions with low publication rates, thus enhancing the diversity of the orthopaedic literature.

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Declaration of competing interest

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