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Reporting of and representativeness of race, ethnicity and socioeconomic status in systemic sclerosis randomized trials: an observational study.

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Abstract

Objectives. To assess how and to what extent socioeconomic status, and ethnicity/race of participants are reported in systemic sclerosis (SSc) randomized controlled trials (RCTs), and to estimate the representativeness of different ethnic/racial groups in SSc-RCTs.

Methods. We searched all published SSc-RCTs indexed in Pubmed. We retrieved information on main features of RCTs published from 2000 onward and recorded for each study whether race/ethnicity was reported; how ethnicity/race was defined and assigned; the number of patients included for each racial/ethnic group. Multivariable logistic regression was used to identify factors associated with race/ethnicity reporting. Proportion of races/ethnicities included in US based SSc-RCTs were examined and compared with US demographic data.

Results. We included 106 studies, mostly conducted in Europe (42%) or North America (25%), published after 2010 (74%), and enrolling a total of 6693 patients. About one-third of studies, provided information about race/ethnicity, with no improved reporting over time. Only two papers reported patient's socioeconomic status. Study location (US or intercontinental) was the only significant factor associated with a better reporting of race/ethnicity in multivariable analysis. In studies where race/ethnicity was reported, White patients were the mostly represented (79%) group, followed by Asian (7%) and African American (6%). In the sensitivity analyses limited to studies from US, underrepresentation of African American patients was observed in 2000 - 2010 period, but not later.

Conclusions. Documentation of race/ethnicity and socioeconomic status is poor in SSc-RCTs. More effort should be put into documenting race/ethnicity and socioeconomic status, and foster diversity in SSc-RCTs.

Significance and innovation

- Race/ethnicity of participants has been reported in only one-third of systemic sclerosis randomized controlled trials published between 2000 and 2021.

- Socioeconomic status has been rarely reported in systemic sclerosis randomized controlled trials.

- Studies reporting race/ethnicity of participants indicate that four of five patients who participated in systemic sclerosis randomized controlled trials were White.

- Representation of Black patients in US-based systemic sclerosis trials has improved over time.

Introduction

Disease's phenotype and response to treatment can vary across racial/ethnic groups.
A common genetic background, different lifestyle, and inequalities in socioeconomic status (1-4), are the main contributing factors. A review of medical interventions approved in United States from 2008 to 2013 has shown that pharmacokinetics, safety, efficacy or dosing differed among ethnic/racial groups in about 21% of the cases (5).

It is therefore of utmost importance that randomized clinical trials (RCTs), the gold standard to estimate the efficacy of medical interventions, clearly report information on race/ethnicity, and more importantly, that patients entering in RCTs are as much as possible representative of the population who will potentially take benefit from the tested intervention (2). Variations in treatment outcomes across subgroups can only be identified if these subgroups are included in RCTs. Achieving diversity in research is not only important for scientific reasons, but has major ethical and social implications (2, 3). A homogeneous distribution across different subgroups of the benefit (and risk) coming from study participation, represents an ethical obligation, and is instrumental to minimize the risk of distrust in health system from the uninvolved population (4).

Systemic sclerosis (SSc) is a rare autoimmune disease characterized by skin and internal organ fibrosis, leading to high morbidity and mortality (6). As in other connective tissue diseases, e.g. systemic lupus erythematosus (7), the epidemiology and severity of SSc vary across different racial/ethnic groups (8-11). In particular, patients of African descendance experience a higher incidence of the disease, earlier onset, more end-organ disease, lower quality of life, and higher mortality than white patients (8, 11).

Little is known about whether trials on SSc adequately report ethnicity/race and socioeconomic status of participants, and how different racial/ethnic groups have been represented in the RCTs conducted so far. We have recently published a study pointing out that the 'imperfect' representativeness of SSc routine care patients in clinical trials was found to be related more to treatment- and safety-related than to demographic criteria (12), but we were not able to assess the inclusiveness of RCTs based on the analysis of patient's ethnicity/race.

We designed this study to assess how and to what extent socioeconomic status and ethnicity/race of study participants are reported in published SSc-RCTs; explore what is the observed versus the expected proportion of SSc patients from different ethnic/racial groups

participating in RCTs; and analyze whether the authors provide data on treatment efficacy/safety according to the ethnicity/race of study participants.

Methods

As the study did not concern human or clinical data, we did not record the protocol on PROSPERO. We followed the reporting guidelines for meta-analyses and systematic reviews of randomized controlled trials, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, with the exception of those relevant only to meta-analyses (eg, risk of bias assessment)(13).

Search strategy

We performed an electronic search of MEDLINE via PubMed on 31 August 2021 to identify RCTs on SSc published since 2000. We used the following combination of free terms and MeSH terms (“CREST”[tiab] OR "Scleroderma, Systemic"[Mesh] OR “Systemic sclerosis”[All Fields] OR “scleroderma”[All Fields]) to identify papers on systemic sclerosis. The Cochrane Highly Sensitive Search Strategy was applied for identifying randomized trials (14).

Eligibility criteria

Inclusion criteria. We included primary reports of SSc-RCTs published since 2000. We defined RCT as a clinical study randomly allocating participants to different interventions.

Exclusion criteria. Studies including patients with scleroderma-like disorders such as morphea, localized scleroderma, or other scleroderma-like diseases (GVHD, toxic-related, etc); secondary publications of RCTs (open-label extension, post-hoc analysis, studies pooling data from more than one RCT); nonrandomized studies; observational studies; meeting abstracts; studies not in English language or published before 2000. We put no restriction for treatment, outcome, or study phase.

Data collection

All retrieved references were downloaded in the free online program Rayyan (Qatar Computing Research Institute, https://www.rayyan.ai), a systematic review web-based application. Two researchers (EC, MI) independently checked each title and abstract to exclude irrelevant papers. The full text article was retrieved to confirm eligibility if information in the abstract was unclear or insufficient. The same reviewers then independently examined full-text articles to determine eligibility. Consensus was reached by discussion in case of disagreement. A third reviewer (DM) was available in case of unsolved disagreement. We documented the primary reason for exclusion of full-text articles.

Data Extraction and Management

One author (EC) extracted the data using a standardized form, and a second author (MI) checked them for consistency. Consensus was reached by discussion. From each study, the following data were obtained: enrolling country(ies), journal impact factor (from Clarivate Analytics)(15), year of publication, funding source (industry- or non-industry funded), phase of development, intervention (pharmacologic, non-pharmacologic), number of patients included, SSc subset studied (diffuse cutaneous SSc, limited cutaneous SSc, both), SSc complication investigated (skin, lung, Raynaud's phenomenon/digital ulcers, gastrointestinal tract, other). Information about the enrolling country(ies) was obtained as follows: first, we checked whether the recruitment centers were reported in the full text; if no explicit information was available, we looked at the location of the institutions linked to the authors; if all the institutions were from the same country, we considered the study to have taken place in that country; in case the authors came from different countries and if information about recruiting centers was lacking in the full-text, we checked the supplementary online material, the published protocols, or the trial registration online repositories (e.g. WHO - International Clinical Trials Registry Platform, Clinicaltrials.gov). If the authors were from institutions in different countries/continents, we considered the study to be international/intercontinental. We considered US-based, a study whose every recruiting centers were in US. A study was considered being industry-funded if the sponsor or one of the collaborators was industry. We recorded whether and which information on patient's socioeconomic status were provided. We considered socioeconomic status related information all the data on individual's place of residence, income, occupation, and educational attainment (1). We also recorded for each study whether race/ethnicity was reported; the definitions used to identify patient groups according the origin (race, ethnicity, race/ethnicity, ancestry, descent, population, other); how ethnicity/race was assigned (patient self-report, perception of health care professionals or researchers, parent/caregiver report, national/government ID, personal/parent birth country, other or unspecified) and the respective categories reported; the reasons for collecting information on race/ethnicity; the number of patients included for each racial/ethnic group; whether the authors reported the main study results across the different racial/ethnic groups included or used race/ethnicity as an adjustment factor for statistical models.

Data analysis

Data were summarized as number (percentage) for qualitative variables and median (interquartile range) for continuous variables. Continuous variables were compared with Student's t-test or Mann–Whitney test, and categorical variables with chi-square test or Fisher's exact test, as appropriate. We used multivariable logistic regression to assess the

impact on race/ethnicity reporting of variables previously shown to impact the quality of trials reporting, e.g. the year of publication (16, 17), journal impact factor (18), study location (continent) (19). The number of SSc patients from each of the main racial/ethnic groups in US (in the periods 2000 - 2009, and 2010 - 2020) was estimated adjusting the observed number of White and Black in US general population retrieved from the Census Bureau (20, 21), with the expected prevalence of SSc in US (224 White and 315 Black SSc patients per million, as reported by Mayes et al.)(22). We then used the chi-square test to compare the estimated White/Black ratio in US general population with the White/Black ratio observed in the sample of patients who had participated in US-based RCTs. The retrieval of the data and their analysis were performed using R 4.1 statistical software (R Development Core Team, Vienna, Austria). All the data and the code used are available at the following Gitlab repository: https://gitlab.com/dmongin/scientific_articles/-/tree/main/ethnicity_SSc_RCTs. A P value ≤ 0.05 was considered significant. Ethical approval was not required (study not involving human participants).

Results

Among the 1085 RCTs identified (flow-chart shown in Figure 1), we included 106 articles, mostly single-country studies (n = 85; 80%), conducted in Europe (n = 44; 42%) or North America (n = 27; 25%), published after 2010 (n = 78, 74%), and enrolling a total of 6693 SSc patients. Studies mostly investigated pharmacologic treatments and included both SSc subsets (limited and diffuse SSc) in half of cases. The median sample size was of 40 patients (IQR 20 - 71.5), with 17 RCTs (16%) having recruited more than 100 patients. Table 1 provides further details regarding trial characteristics.

Reporting socioeconomic status and race/ethnicity in included studies

About one-third of studies (n = 35; 33%), including half of patients studied (n = 3110; 46%), provided information about race/ethnicity. Figures 2A shows the yearly proportion of studies reporting or not race/ethnicity. Only two papers reported patient's socioeconomic status. When reported, the authors define the information they give as race (n = 10/35; 29%), followed by ethnicity (n = 6/35; 17%), or both race and ethnicity (n = 6/35; 17%). 12 papers did not define it. In almost all the included papers, the authors did not explain how and by whom race/ethnicity was determined (self-reported in 2 articles), and they never clarified the reasons for collecting such information (details in online file).

Multivariable logistic regression indicated study location (US-based or intercontinental studies) as the only factor associated with a significantly higher odds of reporting race/ethnicity in (Table 2).

What we know about participation in SSc-RCTs of patients from different race/ethnic backgrounds: time trends and geographical differences

The analysis of all the studies reporting race/ethnicity shows that the group of White patients is the most represented (n = 2450/3110; 79%) (ranging from 49% in 2012 to 100% in 2008), followed by Asian (n = 218; 7%)(ranging from 0% during some years to 17% in 2019) and Black and African American (n = 197; 6%) (ranging from 49% in 2012 to 100% in 2008). In US-based studies, Black patients were significantly more represented (median 7% [IQR 0-16%]) than in studies from other countries (median 0% [IQR 0-4%]), whereas there was no significant difference for other races or ethnicities. Figure 2B presents temporal trends in the proportion of included participants across racial/ethnic groups in the overall sample of studies.

Estimated expected versus the observed proportion of SSc patients entering in US-based RCTs according race/ethnicity

Between 2000 and 2009, the total number of White participants (n = 212) in US-based SSc-RCT was more than 6 times larger than the number of Black participants (n = 34). The White/Black ratio of SSc patients observed in SSc-RCTs was significantly higher than that expected in the sample of SSc patients from US general population during the same period (6.2 vs. 4.9; $P < 0.001$) (Table 3). This under-representation of Black participants was no longer significant during the 2010-2020 period (Table 3).

Outcomes according to race/ethnicity of RCTs participants

In only one paper the authors reported subgroups analyses across ethnic/race groups, and race/ethnicity was never used as an adjustment factor for statistical models.

Discussion

Herein, we have shown that over the two last decades, race/ethnicity of participants was reported in only one-third of SSc published randomized trials, and information on socioeconomic status was almost never available. The extent of race/ethnicity reporting, even if globally low, was higher in studies from US compared to the European ones, and did not increase over time. Reasons for reporting data on race/ethnicity, and the criteria used to define them were rarely disclosed. White patients were globally more represented in SSc-RCTs. In the US, the inclusiveness of Black patients has improved over time.

As for other diseases (23, 24), more should be done to acknowledge race/ethnicity of SSc patients entering in RCTs. This holds true mostly for academic-leaded studies where in less

than one-quarter of cases such information was found; and for Europe-based trials whose reporting of race/ethnicity is much poorer than that of US-based studies. This latter observation is consistent with other reports comparing race and ethnicity documentation in Europe and in the US (19), and is likely to reflect active policies in the US where many initiatives have been launched to achieve the goal of a better reporting (25, 26). The analysis of US-based studies also shows that the extent of race/ethnicity reporting in SSc aligns with that recorded in rheumatoid arthritis (23), but is lower than that observed in studies on systemic lupus erythematosus (9% of papers without information about race/ethnicity)(24), whose prognosis and treatment responses definitely varies across different racial/ethnic groups (7). We have to underscore, however, that this comparison should be interpreted with caution because we used a stricter definition of US-based studies (i.e. studies exclusively enrolling patients in US), compared to that used in studies from rheumatoid arthritis or systemic lupus (i.e. studies with at least one US site were defined US-based).

Of note, only two papers documented socioeconomic status. Lower socioeconomic status is associated with more difficult access to healthcare (27), poor prognosis (28), and the differences in outcomes across racial/ethnic groups are often attenuated after adjustment for this parameter (29). This aspect has been well documented in SSc by a retrospective US-based study showing that the excess of mortality in African American patients in the crude analysis was mitigated after adjustment for socioeconomic factors (29). In this light, as also advocated by the CONSORT statement (30), the availability of information on place of residence, income, occupation, and educational attainment, all encompassed in the definition of socioeconomic status, together with ethnicity/race, are essential to improve the capacity of clinicians to assess the applicability of trial results in everyday clinical practice.

Patients included in SSc-RCTs since 2000 were mostly White. Since the aggregate data covers studies from several continents, in very heterogeneous populations, it is difficult to determine whether this distribution constitutes an under-representation of certain groups in the population under consideration. However, when considering only the US-based studies, and adjusting our estimate for the known prevalence of SSc in US population, we gladly observed an increased representation of Black patients in SSc-RCTs over the last decade. This finding can stem from a number of patient-, physician- and sponsor/funders-related reasons. An increased knowledge about the benefit of taking part in research or a more trustful attitude towards medical health system could have favored trial participation (31). Additionally, the choice of recruitment centers or stakeholder policies to encourage more diverse participation in trials may also have played a role (26). Finally, as briefly mentioned above, a number of initiatives has been launched by the FDA to promote more inclusive participation in trials (25,

26, 32). The relative contribution of each of these aspects is unknown and deserves to be carefully studied.

Only two papers included an explanation about how participant race and ethnicity was determined, as recommended by the latest recommendations (33, 34). It is likely that most studies used a self-reporting strategy, as recommended by the FDA in the US (32), but this remains unknown.

Our study has some limitations. First, the inclusion of RCTs published only in journals indexed in PubMed could have led to exclude lower quality studies, and therefore to overestimate the reporting of race/ethnicity or socioeconomic status. In addition, we were not able to investigate how SSc patients from different origins are represented in international SSc-RCTs conducted in Europe, mainly because the papers did not report the relative contribution of patients at country level. Our analysis evaluating the expected number of SSc patients entering in trials according to the representation of the 2 main race/ethnic groups in US general population has some limitations. First, this analysis is not likely to be generalizable to all studies because it is restricted to RCTs reporting information on patient's race/ethnicity. These studies could differ from those not reporting such information, for example in the degree of inclusiveness. Second, the estimates of the expected number of SSc patients in US has been drawn from a study (22) whose sample could not reflect the entire US population, and does not take into account regional and time variations. Additionally, we limited the analysis of the expected participation in SSc-RCTs to White and African Americans because of the availability of more solid epidemiologic data on SSc for these race/ethnic groups.

This work presents points of strength. We have for the first time analyzed race/ethnicity reporting in SSc-RCTs and raised the question about the extent to which the results of these trials can be generalizable to minorities. Hopefully, this will spur improved trial reporting, and incentivize to plan interventions to make SSc-RCTs more inclusive.

In conclusion, documentation of race/ethnicity and socioeconomic status is poor in SSc randomized controlled trials and the quality of reporting has not improved over time. Despite the increased participation of African Americans in US-based trials in the last decade, more effort should be put into documenting race/ethnicity and including patients in a representative manner. This constitutes a scientific, social and ethical priority.

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Conflict of interest. The authors declare no conflict of interest.

Ethics approval. Not needed.

Contributors

EC, DM, CG, MI contributed to planning and data collection, data quality control, data analysis, and interpretation. They drafted and revised the manuscript critically for important intellectual content and gave final approval of the version to be published. EC, DM, CG, MI contributed to data collection, data quality control, reviewed the manuscript, and provided important intellectual content. EC, DM and MI had full access to the study data. All authors have read, revised, and approved this manuscript and had final responsibility for the decision to submit for publication.

Data sharing

All the data collected and the code used to perform the analysis, create the tables and the figures are openly available at the following repository: https://gitlab.com/dmongin/scientific_articles/-/tree/main/ethnicity_SSc_RCTs.

Tables

Table 1. Main features of included studies.

	Studies, n (%)	*Studies reporting race/ ethnicity, n (%)*	*Studies not reporting race/ethnicity, n (%)*	*P value*
	106 (100%)	35 (33%)	71 (67%)	
Date of publication				0.91
2000-2009	28 (26%)	9 (26%)	19 (27%)	
2010-2020	78 (74%)	26 (74%)	52 (73%)	
Funding				<0.01
Industry	30 (28%)	19 (54%)	11 (15%)	
Non-Industry	39 (37%)	7 (20%)	32 (45%)	
Jointly funded	20 (19%)	8 (23%)	12 (17%)	
Not stated	17 (16%)	1 (3%)	16 (23%)	
Location				<0.01
Europe	44 (42%)	7 (20%)	37 (52%)	
North America	27 (25%)	14 (40%)	13 (18%)	
South America	4 (4%)	0 (0%)	4 (6%)	
Asia	13 (12%)	1 (3%)	12 (17%)	
Africa	3 (3%)	0 (0%)	3 (4%)	
Intercontinental	15 (14%)	13 (37%)	2 (3%)	
SSc subset				0.23
dcSSc	29 (27%)	14 (40%)	15 (21%)	
lcSSc	8 (8%)	2 (6%)	6 (8%)	
both	60 (57%)	17 (49%)	43 (61%)	
Not specified	9 (8%)	2 (6%)	7 (10%)	
Organ complication studied*				0.81
Skin	51 (48%)	18 (51%)	33 (46%)	
Lung	14 (13%)	3 (9%)	11 (15%)	
Gastrointestinal	12 (11%)	4 (11%)	8 (11%)	
Raynaud's/digital ulcers	17 (16%)	5 (14%)	12 (17%)	
No specific complication	16 (15%)	7 (20%)	9 (13%)	
Sample size				0.11
N (median, IQR)	40 [20, 71.5]	43 [20, 121]	38 [19, 61]	
<50	66 (62%)	20 (57%)	46 (65%)	
50-99	23 (22%)	6 (17%)	17 (24%)	
≥ 100	17 (16%)	9 (26%)	8 (11%)	
Intervention				0.29
Pharmacologic	87 (82%)	31 (89%)	56 (79%)	
Non-pharmacologic	19 (18%)	4 (11%)	15 (21%)	

dcSSc. diffuse cutaneous systemic sclerosis; **lcSSc.** limited cutaneous systemic sclerosis; * The sum is >100% (more than one target organ per study could have been studied).

Table 2. Odds ratio for the different terms of the multivariate logistic multivariate regression, predicting the reporting of race and/or ethnicity in the studies considered.

Factor	OR	P value
Year of publication	1.11 [0.983,1.2]	0.10
Impact factor	1.021 [0.978,1.1]	0.43
Continent (reference : Europe)		
North America	6.51 [1.9,22.2]	0.003
Intercontinental	33.61 [5.6,199.6]	<0.001
Other	0.31 [0.03,2.4]	0.23

OR. Odds ratio

Table 3. Estimated versus observed number of White and Black SSc patients entering in US-based RCTs during the period 2000 - 2009 and 2010 - 2020. From left to right column we show: the period considered; the adult White and Black US population according to the US Census; the estimated number of White and Black SSc patients in US, according to epidemiological data from Mayes et al (22); the White/Black ratios in US population and in US-based RCTs reporting race/ethnicity.

	Population, n US Census		Estimated population affected by SSc, n		Patients in US SSc-RCTs, n		Estimated White/Black ratio		
Year	White	Black	White	Black	White	Black	US population	SSc - RCT	P
2000-2009	172.931.742	25.137.964	38.737	7.918	212	34	4.9	6.2	<0.001
2010-2020	190.066.086	31.272.934	42.575	9.851	371	82	4.3	4.5	0.75

Figure 1. Flow-chart of search strategy.

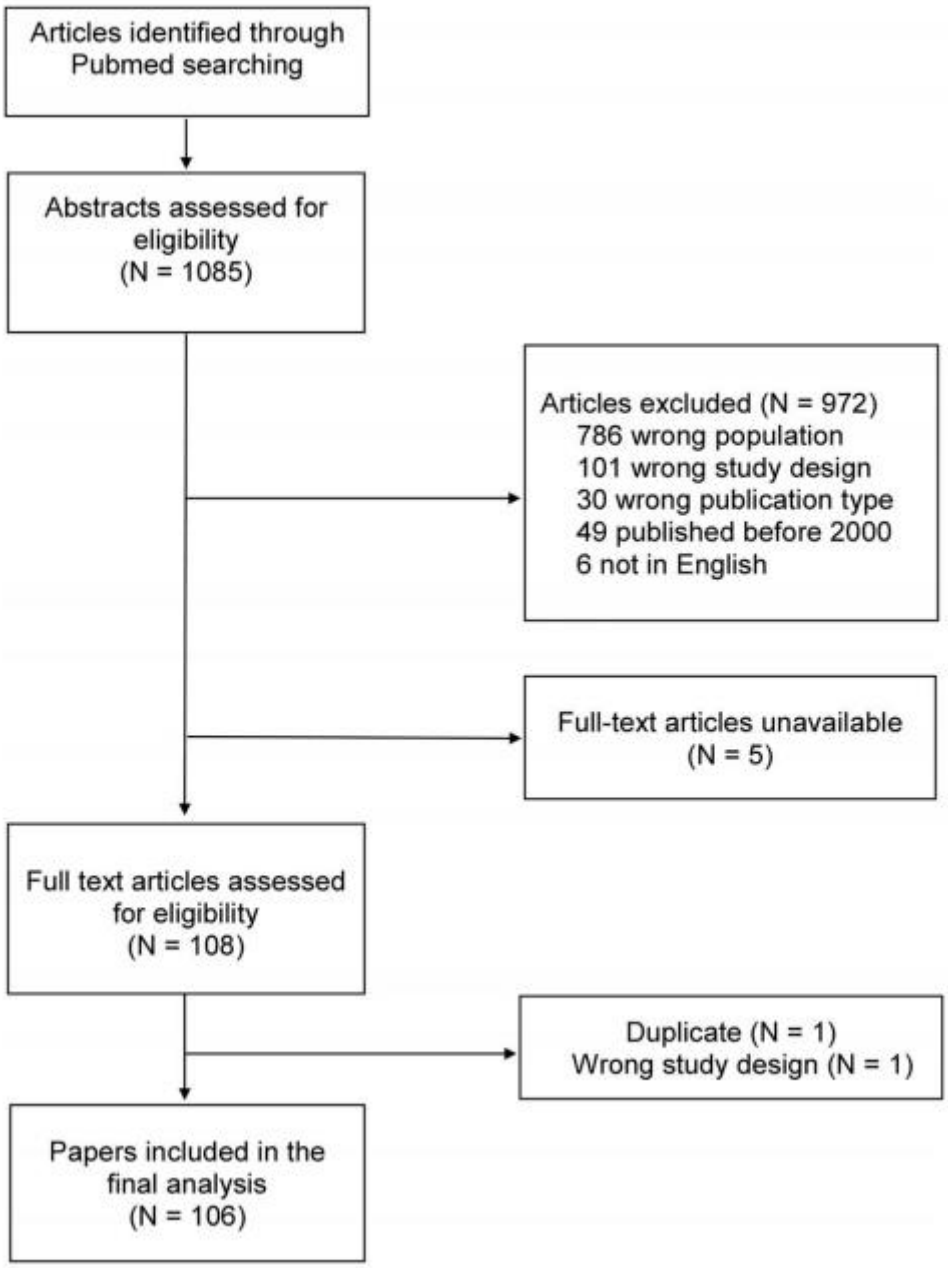
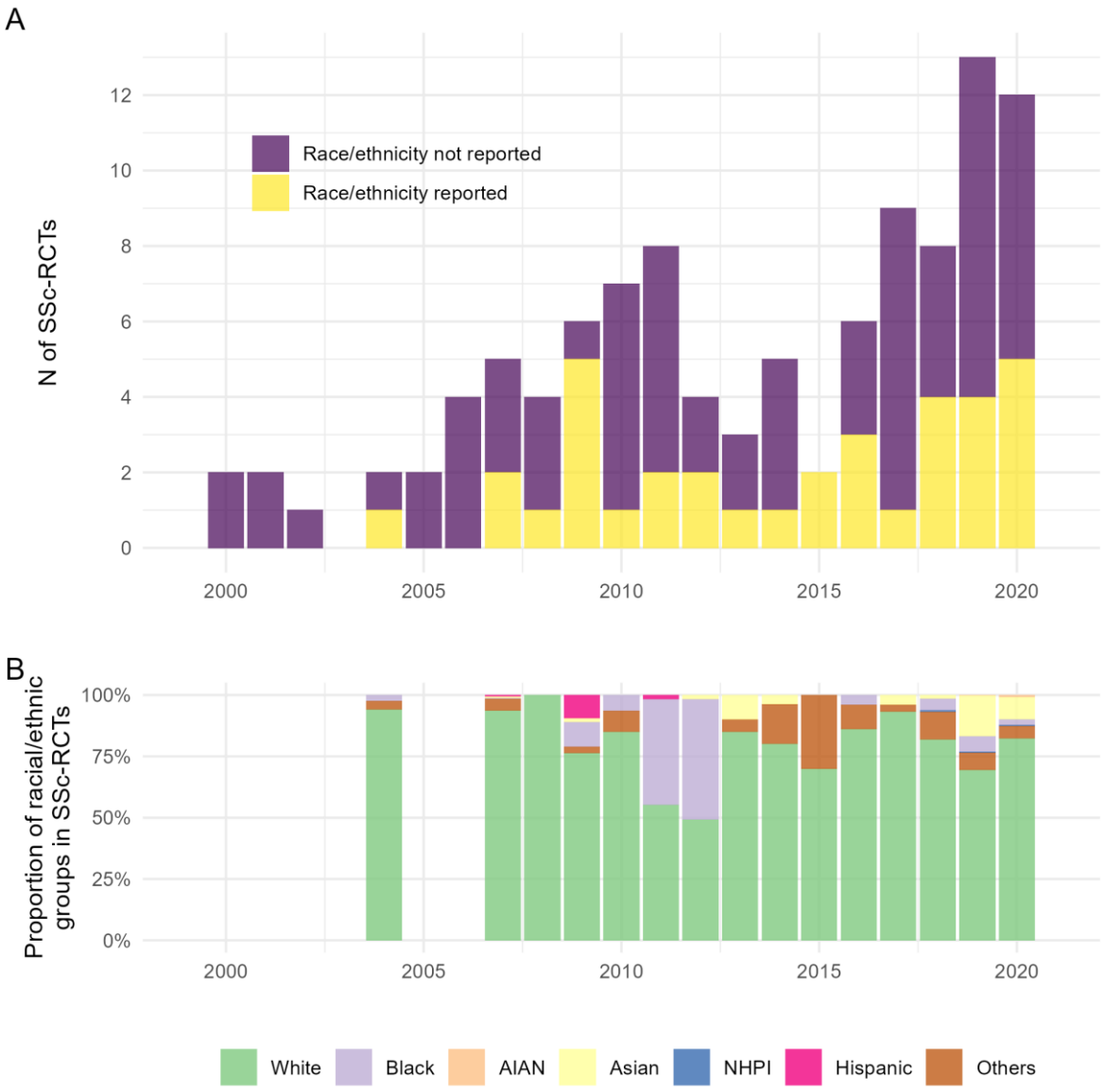


Figure 2. Number of published randomized control trials on Systemic sclerosis (SSc-RCTs) per year, reporting race and/or ethnicity of the enrolled patients. B: proportion of races per year declared in the SSc-RCTs reporting race and/or ethnicity.


A
N of SSc-RCTs
0
2
4
6
8
10
12
Race/ethnicity not reported
Race/ethnicity reported
2000
2005
2010
2015
2020
B
Proportion of racial/ethnic groups in SSc-RCTs
0%
25%
50%
75%
100%
2000
2005
2010
2015
2020
White
Black
AIAN
Asian
NHPI
Hispanic
Others

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