# Gender and racial equity in clinical research for idiopathic pulmonary fibrosis: a systematic review and meta-analysis



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*To the Editor*:

Idiopathic pulmonary fibrosis (IPF) is a devastating interstitial lung disease (ILD) characterised by progressive, irreversible pulmonary parenchymal fibrosis leading to substantial morbidity and shortened survival [1]. Although IPF seems to affect older men predominantly, the true prevalence of IPF in women is difficult to establish, and women may be underdiagnosed while men are overdiagnosed with IPF based on gender alone [2]. Racial and ethnic distribution of IPF has also not been well evaluated in the literature so far, although some studies suggest that non-white patients are diagnosed with IPF at a younger age, and that those of black ethnicity are less likely to receive a diagnosis of IPF [3, 4]. Broad and equitable representation and inclusion of patients with diverse race and gender in clinical research is important, especially for a disease such as IPF, where the prognosis is poor and the effective interventions are few. Equitable representation in research that matches the true distribution of disease in populations allows for improved external validity of findings, leading to increased generalisability of interventions to all patients living with IPF [5].

To our knowledge, no study has assessed the representation of patient race or gender in clinical studies of IPF, specifically in randomised clinical trials (RCTs) of IPF treatments and in observational prospective registry studies. The objective of this systematic review and meta-analysis was to determine what proportion of non-white subjects and women are included in clinical studies of IPF.

A systematic review of the literature was performed using MEDLINE and CENTRAL databases. Two authors (A-C. Jalbert and D. Assayag) selected search terms with the assistance of an experienced librarian. The search was designed to capture 1) randomised controlled trials of treatment for IPF, and 2) population-based observational studies of IPF in prospective registries. Two search strategies (1 and 2) were performed in parallel on 13 August 2020, and updated on 20 April 2021. Titles of studies were first screened for eligibility and inclusion in the meta-analysis, followed by abstracts, then full-text publications. Discrepancies in selection at each step were resolved by consensus. Studies were included if study participants were diagnosed after 2011 (following the publication of the IPF international guidelines) [1], available in English or French, included a minimum of 50 participants, provided clinical information stratified by race or gender, and were either RCTs of IPF treatment or prospective registry studies. When multiple articles presented data from the same registry, the most recently published data was selected, assuming all IPF subjects within that registry were included. Publications reporting only sub-group analyses of previously published data were excluded.

Data on study design, total number of subjects, number of men and women, race, and age of subjects were extracted independently from included studies by two readers (A-C. Jalbert and L. Siafa). Data about the study itself was also captured and included country or continent of origin, year of publication, and the inclusion and exclusion criteria reported by each study. Quality assessment of each study was not systematically performed beyond ensuring the accuracy of subjects, numbers, race and gender, as this was beyond the scope of this review.

Weighted proportions of non-white participants and women included in clinical trials or registry studies were pooled, and stratified by study design. For the meta-analysis, forest plots were provided to illustrate pooled proportions and corresponding 95% confidence intervals using a random effect model [6].



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**Racial and gender-based disparities exist in clinical studies of IPF: 14% of participants in registries or RCTs in IPF are non-white, while the pooled proportion of women in clinical trials is 22%, compared to 27% in prospective registry studies** https://bit.ly/3I6DfnJ

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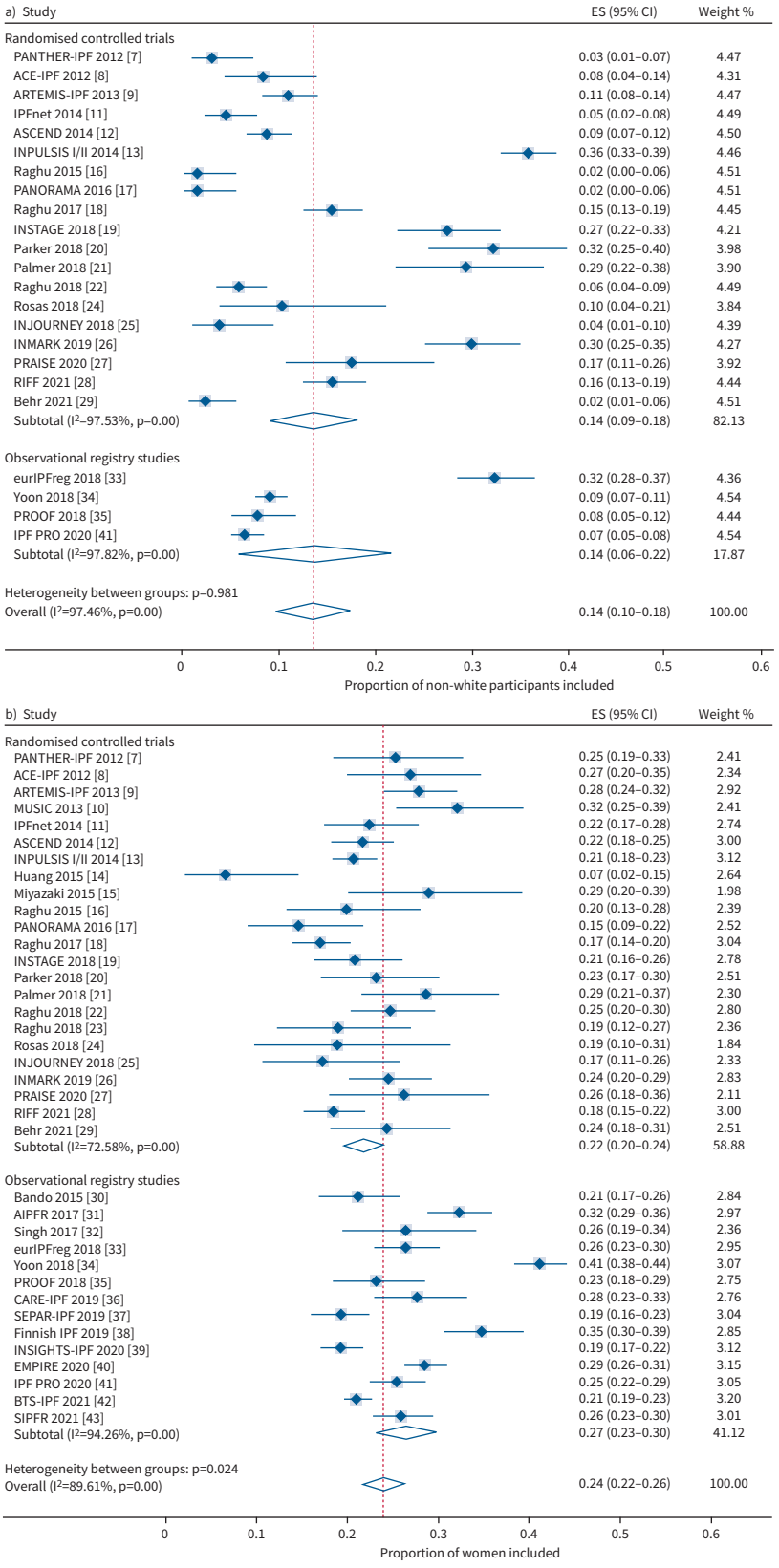


**FIGURE 1** Forest plot of the pooled proportion of non-white participants (a) and women (b) in clinical studies of idiopathic pulmonary fibrosis, stratified by randomised controlled trials and prospective registry studies. The vertical dashed line represents the pool proportion of non-white subjects (14%, panel a) and of women (24%, panel b) across included studies.

Statistical heterogeneity was assessed using the inconsistency ($I^2$) index. Stratified analyses were performed by separating country or continent of origin of the study to identify differences in proportions of non-white patients and women with IPF. Statistical analyses were performed using STATA 14.2 (STATA Corp. LP, College Station, TX, USA).

A total of 37 studies were included in this meta-analysis: 23 were RCTs of IPF treatment, and 14 were prospective registry studies [7–43]. All of the included articles reported gender of participants; however, data on race/ethnicity were reported in 23 of 37 studies (62%). While race was reported in 19 of 23 RCT (83%), it was reported in only four of 14 (29%) registry studies. The weighted pooled proportion of non-white individuals in IPF studies was 14%, ranging from 3% to 32% (figure 1a), with no significant difference between RCTs and registry studies. Studies originating from North America had a lower proportion of non-white participants (7%, 95% CI 5% to 9%) compared to studies from Europe (17%, 95% CI 15% to 20%) or international studies that included Asia or Australia (23%, 95% CI 18% to 29%).

The weighted pooled proportion of women in IPF studies was 24%, ranging from 15% to 41%. There was a trend towards a greater inclusion of women in registry studies, with 27% female participants (95% CI 23% to 30%) compared to RCTs, which had only 22% of women enrolled (95% CI 20% to 24%), as illustrated in figure 1b. Geographic area or country of origin did not impact proportion of female participants.

This systematic review and meta-analysis highlights that non-white subjects are underrepresented in clinical studies of IPF, but also that race is frequently underreported by researchers and unpublished, especially in registry studies. Women seem to be more fairly represented in RCT when compared to registry studies, although there was still a 5% difference between study types. In addition, there was wide variability across studies and high heterogeneity, with some clinical trials having very low proportion of women participants. Women have been shown to be underrepresented in clinical trials of a wide range of other diseases as well [44].

In order to determine how closely recruitment into clinical trials of IPF treatment matches true, real-world population diversity, study enrolment should be compared to the best estimate of IPF prevalence and proportions of women and non-white patients. However, these data are very challenging to obtain, as there is no gold standard for estimating IPF prevalence. Population-based studies using administrative data and diagnostic codes have inherent biases of misclassification and misdiagnosis. Registry studies likely better represent the breadth of patients with IPF, but enrolment in registries is also subject to biases, such as referral bias to an ILD centre, or even race- and gender-based biases. Studies have shown that non-white patients in North America are less likely to participate in clinical studies due to mistrust of research, systemic bias, and social and structural barriers [45].

We propose a few steps that researchers can take to ensure equitable recruitment into clinical studies. Participant-specific interventions include systematically offering registry enrolment to all patients seen in ILD clinics, offering reimbursement of incurred costs for study participation, providing access to medical translators when necessary, and recruiting clinical trial participants from within diverse registries. Study-specific interventions are also important. We propose to include quotas for enrolment of racial minority participants in clinical trials, having gender- and racially diverse research team members, and favouring multicentre, multinational collaborative studies, when possible. Finally, we propose to make gender and race reporting mandatory in all peer-reviewed publications of clinical research. With a concerted effort, the ILD community can work towards greater, more equitable inclusion of research participants to represent the true diversity of patients who live with IPF worldwide.

**Annie-Claude Jalbert[1], Lyna Siafa[2], Agnihotram V. Ramanakumar[3] and Deborah Assayag[1,3]**

[1]Dept of Medicine, McGill University, Montreal, QC, Canada. [2]Faculty of Medicine, McGill University, Montreal, QC, Canada. [3]Research Institute McGill University Health Center, McGill University, Montreal, QC, Canada.

Corresponding author: Deborah Assayag (deborah.assayag@mcgill.ca)

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