



## Early View

Research letter

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# Gender and Racial Equity in Clinical Research for Idiopathic Pulmonary Fibrosis: a Systematic Review and Meta-Analysis

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Research Letter

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**Take home message:** Racial and gender-based disparities exist in clinical studies of idiopathic pulmonary fibrosis (IPF): non-Whites make up 14% of participants in registries or randomized clinical trials of IPF, while the pooled proportion of women in clinical trials is 22%, compared to 27% in prospective registry studies.

Competing interests

ACJ, LS and AVR report no competing interests.  
DA reports grants and personal fees from Boehringer-Ingelheim Canada and personal fees from Roche Canada, outside of submitted work.

Dear Editors,

Idiopathic pulmonary fibrosis (IPF) is a devastating interstitial lung disease (ILD) characterized 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-Whites are diagnosed with IPF at a younger age, and that Blacks are less likely to receive a diagnosis of IPF.[3, 4] Broad and equitable representation and inclusion of patient 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 more generalizability 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 randomized 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-Whites and women are included in clinical studies of IPF.

## Methods

A systematic review of the literature was performed using MEDLINE and CENTRAL databases. Two authors (ACJ, DA) selected search terms with the assistance of an experienced librarian. The search was designed to capture A) randomized controlled trials of treatment for IPF and B) population-based observational studies of IPF in prospective registries. Two search strategies (A and B) were performed in parallel on August 13, 2020, and updated on April 20, 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 RCT 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 analysis of previously published data were excluded.

#### *Data Extraction and Quality Assessment*

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 (ACJ and LS). Data about the study itself was also captured and included country or continent of origin, year of publication, 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.

#### *Statistical analysis*

Weighted proportions of non-Whites 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 [CIs] using a random-effect model.[6] 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-Whites and women with IPF. Statistical analyses were performed using STATA 14.2 (STATA Corp. LP, College Station, Texas, USA).

## RESULTS

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 race data were reported in 23 of 37 studies (62%). While race was reported in 19 of 23 RCT (83%), it was found in only 4 of 14 (29%) registry studies. The weighted pooled proportion of non-Whites in IPF studies was 14%, ranging from 3% to 32% (**Figure 1A**), without 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.

## DISCUSSION

This systematic review and meta-analysis highlights that non-Whites 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 the true, real-world population diversity, study enrollment should be compared to the best estimate of IPF prevalence and proportions of women and non-Whites. 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 enrollement in regsitries is also subject to biases such as referral bias to an ILD center, or even race- and gender-based biases. Studies have shown that non-Whites 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 to systematically offer registry enrollment to all patients seen in ILD clinics, offer reimbursement of incurred costs for study participation, 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 enrollement of racial minority participants in clinical trials, having gender- and racially-diverse research team members, and favoring multicenter, 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 world-wide.

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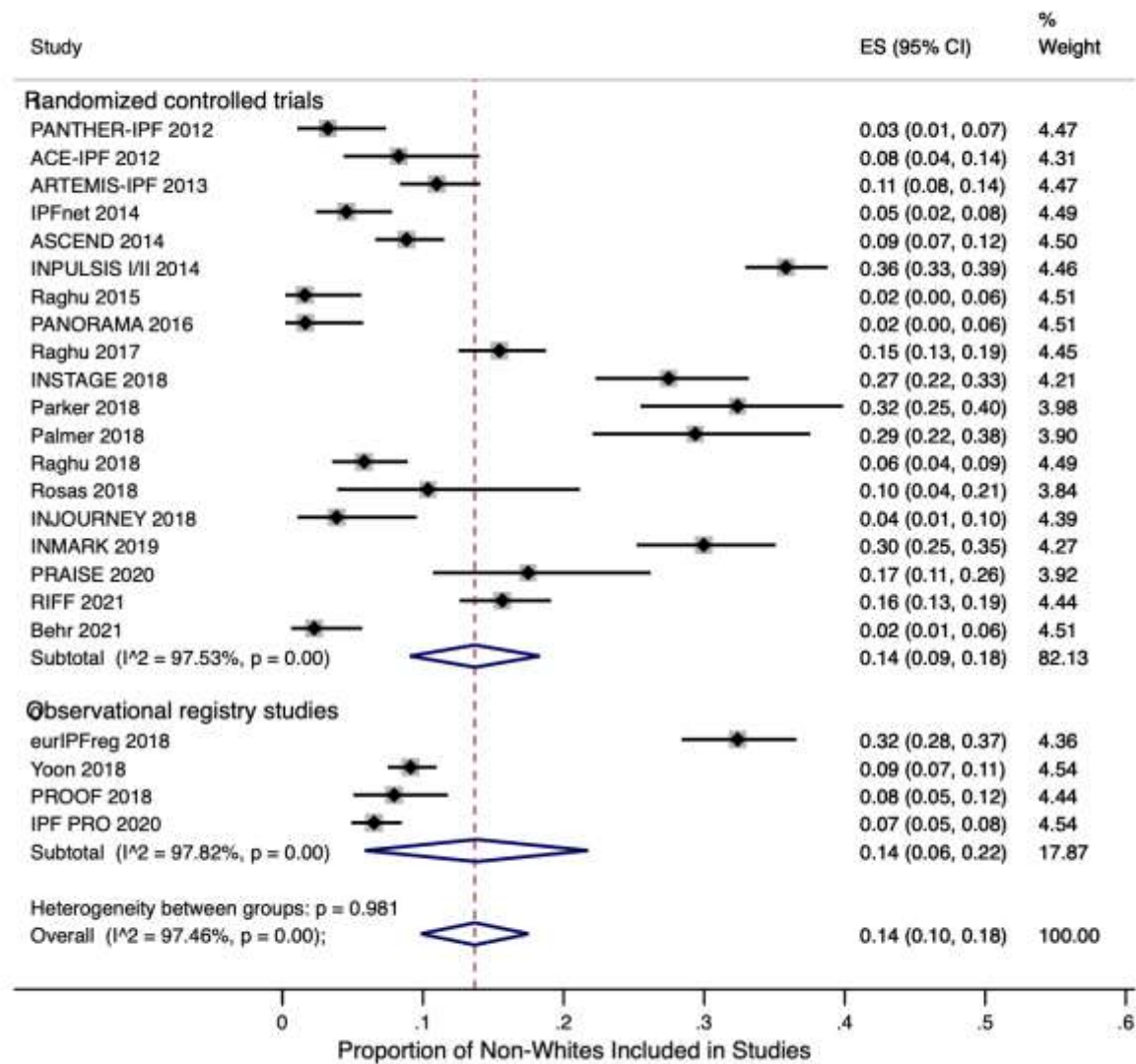
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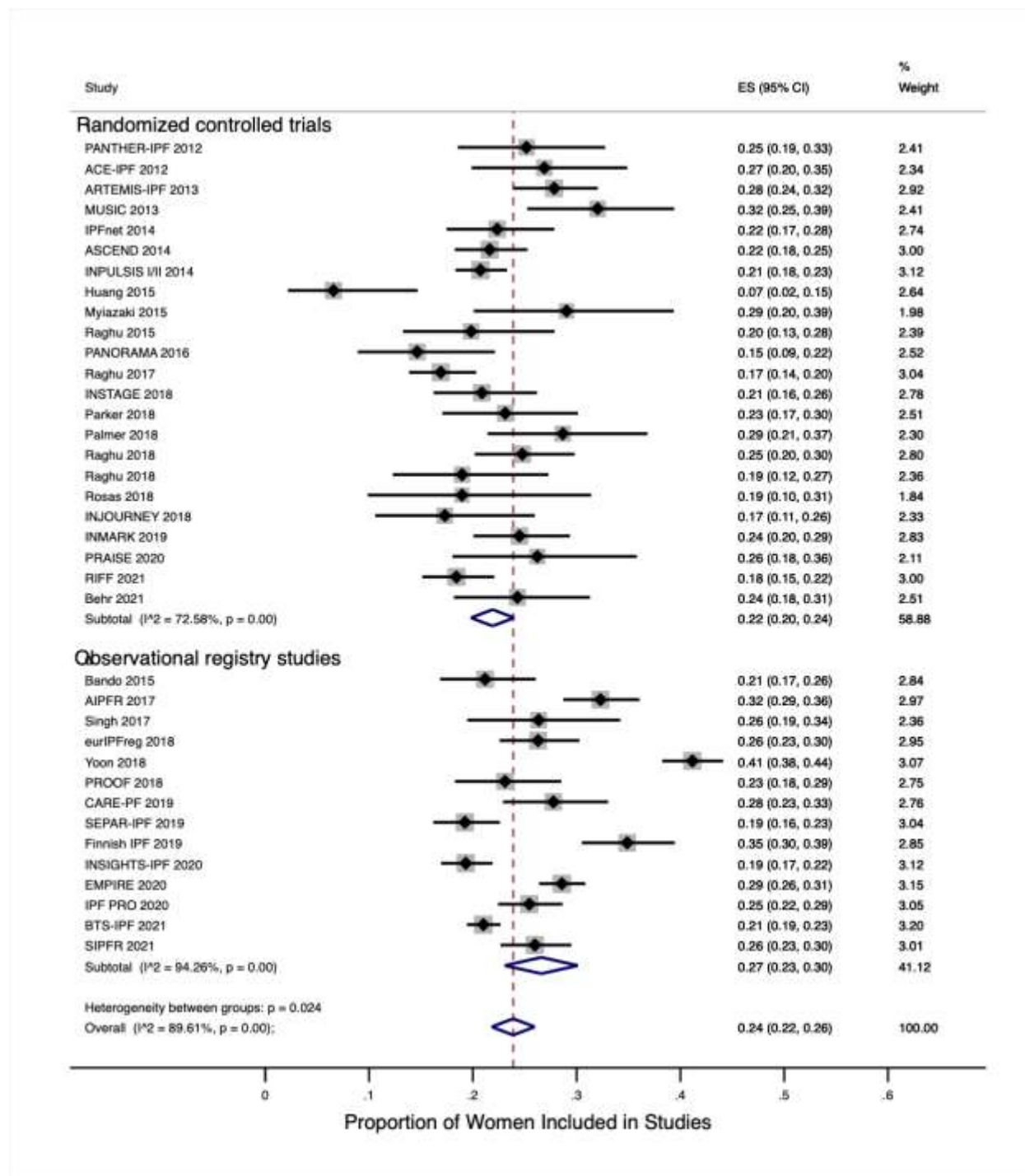
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**Figure 1.** Forest-plot of the pooled proportion of non-White participants (A) and women (B) in clinical studies of IPF, stratified by randomized controlled trials and prospective registry studies. The vertical dashed line represents the pool proportion of non-Whites (14%, panel A) and of women (24%, panel B) across included studies.