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Applicability of trials in rheumatoid arthritis and osteoarthritis: A systematic review and meta-analysis of trial populations showing adequate proportion of women, but underrepresentation of elderly people

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ABSTRACT

Objectives To evaluate whether elderly people and women are adequately represented in randomized controlled trials (RCT) in rheumatoid arthritis (RA) and osteoarthritis (OA).

Methods Four systematic searches in MEDLINE yielded RCT in RA and OA on any intervention published in 2016 and 2017 and population-based studies (PBS) in RA and OA published between 2013 and 2017. Random effects meta-analyses estimated the pooled proportion of elderly people (defined as being ≥65 years old), the mean age, its standard deviation (SD), and the proportion of women stratified by disease (RA and OA) and study type (RCT and PBS). Stratified estimates were subsequently compared.

Results 265 RCT comprising 51,240 participants and 53 PBS comprising 523,630 participants were included. In both RA and OA, RCT included lower proportions of elderly people than PBS: RA –0.18 (95% confidence interval –0.22 to –0.13); OA –0.20 (–0.30 to –0.09); had lower mean ages: RA –5.2 years (–6.8 to –3.5); OA –4.7 years (–7.5 to –2.0); and smaller SD: RA –1.9 years (–2.6 to –1.3); OA –2.7 years (–4.2 to –1.2); (all comparisons: $p \leq 0.001$). Proportions of women were comparable in RCT compared to PBS in both RA and OA.

Conclusions While women are adequately represented in RA and OA trials, the elderly are underrepresented, probably limiting applicability of current evidence to this growing subgroup. It is urgent to improve the inclusion of elderly people in clinical trials and study age as a determinant for outcome.

Systematic Review Registration PROSPERO (CRD42018085409)

Keywords Applicability, Generalizability, Elderly, Women, Rheumatoid Arthritis, Osteoarthritis

INTRODUCTION

Randomized controlled trials (RCT) shape the evidence base and are generally considered the gold standard in clinical research. However, their results are not necessarily applicable to the whole population suffering from the diseases under investigation.[1] Applicability (sometimes called generalizability or external validity) can be defined the extent to which 'available research evidence can be directly utilized to answer the healthcare questions at hand'.[1, 2] It is a key factor in the translation of clinical research to the real world.[1] There are several characteristics in which trial populations may differ from real-world patients and which therefore affect trial result applicability, e.g., sex, age, and comorbidities.[1]

Despite the considerable rise in numbers of elderly people – 'elderly' commonly defined as aged 65 years or more – in countries all over the world,[3] this group is underrepresented in clinical trials across various medical fields.[4-11] Such underrepresentation bears considerable risks as elderly differ from younger people in several aspects, including pharmacodynamics and pharmacokinetics, comorbidity, polypharmacy, and physical performance.[12, 13] All of these may affect the potential for benefit and usually increase the risk of harm. Women are underrepresented, too, with similar implications.[1, 7, 14-16]

Empirical evidence on the representation of elderly people and women in rheumatologic clinical trials is lacking. Rheumatoid arthritis (RA) and osteoarthritis (OA) are two of the most common chronic rheumatic diseases and major contributors to global disability.[17-22] Both tend to occur predominantly in elderly people – and mostly in women.[17-23] We therefore investigated whether RCT reflect these tendencies, possess similar characteristics in age distribution measures and include proportions of elderly people and women comparable to real-world data obtained by population-based studies (PBS) including registries. Additionally, we assessed whether there are associations between proportions of elderly people and industry funding and different types of intervention.

METHODS

This study is part of the GLORIA project and trial (Glucocorticoid low-dose outcome in rheumatoid arthritis study; http://www.gloriatrial.org/; registered on http://clinicaltrials.gov/; identifier NCT02585258).[24] It conforms to the *PRISMA* (for systematic reviews of interventional studies) and *MOOSE* (for systematic reviews of observational studies) guidelines (see supplementary file for research checklists).[25, 26] The prespecified protocol (see supplementary file) was preregistered with the protocol registry for systematic reviews, PROSPERO (CRD42018085409).

Abbreviations
RCT – Randomized controlled trial; RA – Rheumatoid arthritis; OA – Osteoarthritis; PBS – Population-based study; SD – Standard deviation

Search strategy

Using the biomedical database MEDLINE (via PubMed), we conducted separate searches for RCT and PBS in RA and OA through 31 December 2017. We limited the search for RCT to trials published from 1 January 2016, whereas our search for PBS began with 1 January 2013 to ensure sufficient real-world data. Additionally, we performed a hand search for relevant publications including a scan of the references of major guidelines and reviews of RA and OA. We decided *a priori* that we would not attempt to contact study authors or include unpublished studies. For exact search strings, which we developed with researchers experienced in systematic reviews and meta-analyses, please consider our study protocol.

Eligibility criteria

All studies (both RCT and PBS) had to report the mean or median age at baseline of all included patients/populations. Corresponding to GLORIA collaborators, we excluded publications in languages other than English, French, Spanish, German, Italian, Hungarian, Portuguese, Dutch, Slovakian, and Romanian. We defined PBS as observational studies fulfilling one of the following criteria: study objective being the determination of RA or OA prevalence in the general population; studies with other objectives, but undertaken in prevalent RA or OA populations without apparent selection mechanisms as to age or gender; or studies in ongoing RA or OA registries.[27] For additional specifications please refer to our study protocol.

Two reviewers (AP and TB) independently selected the studies. After removing duplicates, they screened the articles by title and abstract, and assessed potentially eligible articles in full-text. They achieved consensus by discussion when necessary.

Data extraction

We extracted the data using predefined data extraction sheets which we derived from the Cochrane Collaboration's recommendations for data extraction and modified for our purposes.[28] We dichotomized information on funding into *any industry funding* and *no industry funding*, and categorized treatment modalities into *pharmacological*, *surgical*, *physical/physiotherapeutic*, and *psychological*.

Risk of bias

Two reviewers (AP and TB) independently assessed risk of bias of the included PBS using the newest version of the *Joanna Briggs Institute Critical Appraisal Checklist for Prevalence Studies*.[29, 30] Discussion resolved rating discrepancies. Regarding RCT, our sole outcomes were baseline

characteristics, so we considered quality appraisal not to be necessary. We did not assess risk of bias across studies, e.g., publication bias,[25] since, in our opinion, there is no reason to believe that any of our study variables makes studies more or less likely to get published.

Data synthesis

We used R (R Foundation for Statistical Computing, Vienna, Austria) with packages *meta* and *metafor* and Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA, USA) software for data extraction, management, and analysis. The format of reporting results conforms to guidelines recently proposed by one of us.[31]

We either extracted the proportion of elderly participants from the research manuscript or estimated it. In the latter case, we estimated the proportion utilizing an established method under assumption that age is distributed normally, but with truncation as trials employ upper and/or lower age limits as exclusion criteria.[8, 9, 32] The model considers studies to be either singly (assuming a lower age limit of 18 years if not reported otherwise) or doubly truncated.

We conducted restricted maximum likelihood random effects meta-analyses on each of our four outcomes: the proportion of elderly people (i.e., aged ≥65 years), the mean age, its SD (as a measure of dispersion), and the proportion of women (all performed separately for RCT and PBS and stratified by disease). We subsequently compared the results and tested the differences for statistical significance with two-sample Z-tests.[33] We evaluated heterogeneity with Cochran's Q-statistic and present it as an I^2-value, which estimates the total percentage of variance across studies due to heterogeneity rather than statistical error.[28, 34] In RCT, we additionally assessed whether representation of elderly people differed across funding and intervention types through meta-regression analysis including a factor for funding or intervention and testing for moderators with Wald-type tests.[35] We set the two-sided significance level α at .05. For additional specifications concerning data synthesis please refer to our study protocol.

RESULTS

Search results

Our database search yielded 3,065 results (**Figure 1**). We identified 11 additional articles by hand search. Of these 3,076 publications, 265 RCT and 53 PBS were finally deemed eligible (see supplementary file for a list of all included studies).

Study characteristics

RCT included 51,240 patients (30,410 RA and 20,830 OA patients; **Table 1**). The majority of included RCT originated from Europe and Asia, although most RA RCT were not limited to one region. In RA RCT, industry funding was more prominent than in OA RCT. None of the studies that explicitly excluded elderly patients provided a reason for doing so. Seven RCT (3%) reported the proportion of elderly participants, and five RCT (2%), all on OA, assessed the influence of participant age on outcomes.

PBS included 523,630 patients (449,329 RA patients and 74,301 OA patients). Just like RCT, most PBS were conducted in Europe and Asia. No PBS reported the proportion of elderly participants.

Risk of bias assessments are presented in the supplementary file. In 38% of PBS, authors did not report the number of people willing or refusing to participate, and in 34% it was unclear whether data analysis was performed with sufficient coverage of the identified sample. Other potential sources of bias include ambiguity regarding disease identification methods (30%) and execution of these (21%). The sample size was considered low in 25% of PBS. Overall, studies in healthcare and insurance databases had the lowest percentage of questions answered "*no*" (0% of questions).

Comparison of RCT and PBS

In both RA and OA, RCT included significantly fewer elderly people than did PBS (**Figure 2**): RA –0.18 (95% confidence interval –0.22 to –0.13); OA –0.20 (–0.30 to –0.09); and had significantly lower mean ages: RA –5.2 years (–6.8 to –3.5); OA –4.7 years (–7.5 to –2.0). RCT also had smaller SD: RA –1.9 years (–2.6 to –1.3); OA –2.7 years (–4.2 to –1.2); (all comparisons $p \leq 0.001$). In both RA and OA, RCT included similar proportions of women compared to PBS: RA 0.02 (–0.01 to 0.05); OA –0.04 (–0.10 to 0.03). Heterogeneity was considerable in all meta-analyses with I^2 values between 96% and 100%. Individual meta-analyses are presented in the supplementary file.

Stratified analyses

Funding source did not influence the deficit of elderly in RCT (RA, $p = 0.82$; OA, $p = 0.26$; **Table 2**). Type of intervention did influence the deficit, but only in RA (RA, $p = 0.02$; OA, $p = 0.60$).

DISCUSSION

We found the elderly to be underrepresented in RA and OA trials; mean ages and the variation in age (SD) were lower in RCT than in PBS. RCT included proportions of women comparable to real-world

settings. While the proportion of included elderly patients showed no association with industry funding, it differed in RA RCT but not in OA RCT depending on the intervention.

Intense and successful research in rheumatology has led to crucial discoveries in disease mechanisms and both diagnostic and therapeutic management over the last two decades. While all this research surely has and will continue to benefit most patients, our study suggests applicability to the large subgroup of elderly patients may be limited.

Underrepresentation of the elderly in medical science is not a new phenomenon.[10] Since its documentation in cardiology in the 1990s,[7] it has been confirmed in renal, neurological, and oncological diseases, in diabetes, and in surgical procedures (see supplementary file for a list of studies on this subject). Current guidelines still widely rely on trials lacking applicability to elderly patients.[11, 16]

Various national and international institutions have acknowledged this problem and have undertaken efforts to tackle this issue. The U.S. food and drug administration (FDA) requires drug sponsors to report trial data by age,[36, 37] but low numbers of elderly in clinical trials diminish the statistical power to detect significant differences between them and their younger counterparts in both efficacy and safety.[37, 38] The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use and the European Forum for Good Clinical Practice have issued guidance for research in the geriatric population.[38, 39] It has been demanded repeatedly that institutional review boards and journals pay attention to whether applicability of trial results concerning age is assured.[7, 40] All the same, elderly people still seem to be underrepresented in clinical trials.

In RA and OA trials, two publications suggested underrepresentation of the elderly: In RA, patients in RCT of etanercept, rituximab, and tocilizumab were younger than those enrolled in observational studies on these agents.[41] In OA, 38% of trials published before 2007 did not have patients above the age of 80 years, and 11% explicitly excluded elderly patients.[42] In our study this proportion was more pronounced at 36%.

It remains unclear why the elderly are actively excluded by trials installing upper age limits. No trial in our study justified doing so, although justification of exclusion criteria has been demanded repeatedly.[5] In trials, investigators generally aim for homogeneous study samples and might fear higher rates of (serious) adverse events and drop-outs in aged people.[4, 43, 44] Other mechanisms

that keep the elderly from participating are exclusion criteria related to age such as comorbidities, strict organ function criteria, or performance status.[45, 46] Physician- and patient-level factors that add to this are, amongst others, physicians being reluctant to include elderly people due to fear of increased toxicity, and elderly people themselves having difficulties judging benefits and risks.[45-47]

We did not find a statistically significant association between industry funding and the proportion of elderly people. Previous studies have come to varying results, with industry funding being associated with higher (in heart failure trials), lower (across trials of all specialties), and no different rates (in trials on statins, non-steroidal anti-inflammatory drugs, and type 2 diabetes mellitus) of explicit exclusion of elderly people.[4, 5, 48, 49] The lack of influence of type of intervention in OA trials (in contrast to RA trials) is surprising, since adequate interventions (e.g., endoprosthetic surgery) depend on the severity of the disease (e.g., late-stage OA) and could therefore be associated with age. To sum up, evidence is ambiguous, but associations in both respects might vary between diseases.

Numerous attempts have been made to analyze how age affects trial outcomes, and studies doing so have yielded quite heterogeneous results. As one example, thrombolytic and interventional therapy is associated with higher mortality in older patients with myocardial infarction, while the elderly had similar response and survival rates in trials on lung and breast cancer.[50-53] Recent research suggests lower response rates to biologicals in elderly RA patients and a diminished benefit-to-risk ratio.[54-56] Of all 265 RCT included in our study, only five analyzed age as a determinant for outcome. Their results were conflicting: In two studies, older participants profited less or had worse outcomes than younger ones,[57, 58] but experienced a more pronounced treatment effect in another.[59]

In contrast to the past and the present in other medical specialties,[7, 14-16] we did not find women to be underrepresented. In fact, women make up the majority of patients included in current RA and OA clinical trials. Generally, this is consistent with the distribution of RA and OA in men and women. With increasing age, however, gender disparities in both diseases decrease.[60, 61] Thus, it should be underlined that current evidence is especially sparse regarding elderly men.

Both efficacy and safety data must be interpreted with caution if they stem from study populations which differ from general diseased populations in age or sex (or disease duration, or disease severity, etc.). In the past, young Caucasian males were usually considered the ideal study subjects, and pharmacodynamic and -kinetic differences in other subpopulations were paid little attention, as was the case with differing comorbidities or drug interactions (think of polypharmacy in the elderly).[10] Drugs were approved without sufficient study in elderly people, non-whites, or women.[10]

An infamous example of this phenomenon is benoxaprofen, a drug introduced in the 1980s to treat arthritic conditions.[62] Benoxaprofen had previously been studied in large clinical trials. However, its licenses were suspended only two years after launch because of unacceptable rates of (serious) adverse events in 'real-world' patients, including deaths – mostly in the elderly, who had been studied very little before.[62] Researchers later found tremendous pharmacological differences between the elderly and younger (or – as the researchers put it – *'normal'*) patients.[63]

Researchers should investigate the effect of age and other covariates such as sex on outcomes routinely on trial-level data. However, this is only useful when adequate numbers of, e.g., elderly people are included in clinical trials.[37, 38] The current meta-analysis was performed under the umbrella of the GLORIA project, which also includes a trial focusing specifically on RA patients aged 65 or over.[24] While studies aimed at younger populations might measure outcomes and define endpoints that are less relevant to elderly people, performing trials focused on the elderly is an option. This option takes into consideration that some outcomes are particularly valuable for older patients.[64-66] Such relevant outcomes include functional ones (e.g., quality of life) instead of solely disease-specific ones.[64-66] Factors that impede inclusion and retention of the elderly (at trial-, physician- and patient-level) have been identified and should be countered.[45-47, 67-70] Another option is to replace the traditional explanatory RCT by a pragmatic design: for example, the GLORIA trial has very 'relaxed' eligibility criteria, uses routinely collected data where possible, and takes place in the routine clinical setting.[71] Yet another option is to construct and conduct RCT on the foundation of ongoing observational studies. These so-called registry-based RCT usually cover real-world settings and go with higher applicability as well.[72]

To our knowledge, this is the first study to prove and quantify underrepresentation of elderly people in rheumatology by comparing RCT and PBS. Strengths include the high number of studies and participants, a systematic literature search not limited to the English language, and protocolized execution. Study selection and risk of bias assessment were performed independently by two authors to reduce the risk of systematic bias. We excluded RCT that only presented baseline characteristics from study finishers, so our results should not be affected by the possibility that older patients may be prone to dropping out.

This study also has limitations. We have restricted our search to MEDLINE, but it is unlikely that our results would differ by including trials indexed elsewhere only. Furthermore, with our search restricted to RCT published within the last two years, our analyses reflect only the current situation, but we feel

that is most relevant. Finally, the assessment of the 'real' prevalence is dependent on the quality of population-based evidence, and some studies had flaws. Nonetheless, we are convinced these flaws do not cast doubt on our overall results.

We did encounter considerable heterogeneity in all meta-analyses. Some heterogeneity will be due to our 'relaxed' eligibility criteria, which led to inclusion of a variety of study types and interventions. In RCT, heterogeneity may be caused by studies being aimed at or explicitly excluding elderly people, women, or patients in a certain disease stage. Regarding both RCT and PBS, heterogeneity could also be explained by varying demographics across different regions. Overall, though, only three RA PBS and one OA PBS included proportions of elderly people that were smaller than pooled RCT estimates. Accordingly – since meta-analytical estimates were consistent — we did not perform additional sensitivity analyses.[34] Finally, we had to estimate proportions of elderly people in the majority of RCT and PBS. However, our method to do so is established and has been applied repeatedly.[8, 9]

CONCLUSIONS

Our study proves that elderly people, but not women, are significantly underrepresented in randomized clinical trials on rheumatoid arthritis and osteoarthritis, raising serious concerns about applicability of their results. It is urgent to improve the inclusion of elderly people in clinical trials and to study age and sex as a determinant for outcome.

FOOTNOTES

Contributors

AP, YP, and FB had the idea for the study. AP, YP, MB, RC, and FB developed the study design. AP and TB performed the study selection and risk of bias assessment. AP extracted the data. AP, SMN, RC, and FB analyzed and interpreted the data. All authors critically revised the manuscript and approved the final version for submission. FB is the guarantor, had full access to all the data, takes responsibility for the integrity of the data and the accuracy of the data analysis, and had final responsibility for the decision to submit this article for publication. All authors have read, and confirm that they meet, ICMJE criteria for authorship.

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Competing Interests

AP, TB, MB, and FB have received grants from the European Union (Horizon 2020 Framework Programme for Research and Innovation) during the conduct of the study. YP and SMN have nothing to disclose. RC reports non-financial support from board membership, grants from consultancy (AbbVie, Amgen, Axellus A/S, Biogen, Bristol-Myers Squibb, Cambridge Weight Plan, Celgene, Eli Lilly, Hospira, MSD, Norpharma, Novartis, Orkla Health, Pfizer, Roche, Sobi, Takeda), personal fees from employment (Research Unit for Musculoskeletal Function and Physiotherapy, Institute of Sports Science and Clinical Biomechanics, University of Southern Denmark), non-financial support from expert testimony, grants/grants pending (Axellus A/S, AbbVie, Cambridge Weight Plan, Janssen, MSD, Mundipharma, Novartis, and Roche), payment for lectures including service on speakers bureaus (Abbott, Amgen, Axellus, Bayer HealthCare Pharmaceuticals, Biogen Idec, Bristol-Myers Squibb,

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Ethics Approval

Not required.

Data Sharing

FB is willing to examine all requests for the full dataset during a period of 5 years from the date of this publication. The GLORIA steering committee will be involved in case of query about access.

Transparency

The guarantor (FB) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained.

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TABLES

Table 1. *Study characteristics.*

	PBS (n = 53)		RCT (n = 265)	
	RA (n = 42)	**OA (n = 11)**	**RA (n = 102)**	**OA (n = 163)**
Location				
Europe	38	27	28	39
Asia	30	36	23	26
Multiple	5	9	41	1
North America	10	9	3	18
Oceania	2	0	1	10
Central and South America	12	18	3	4
Africa	2	0	1	3
Intervention				
Pharmacological	NA	NA	82	25
on biologic agents[a]			69	7
on biosimiliars[b]			16	0
Physical/physiotherapeutic			9	32
Surgical			0	22
Psychological			4	4
Other			5	18
Design[c]				
Cross-sectional	41	73	NA	NA
Cohort (including registries)	41	9		
Healthcare and insurance databases	21	18		
Funding				
No industry funding	67	82	30	64
Any industry funding	26	18	67	24
Not available[d]	7	0	3	12
Upper age limit				
Not present	NA	NA	72	64
Present			28	36
Justification given			0	0
Sample size[e]	1,107 (409 - 8,998)	696 (161 - 11,111)	212 (72 - 386)	81 (48 - 164)

Numbers are percentages if not stated otherwise. PBS, population-based studies, RCT, randomized controlled trials, RA, rheumatoid arthritis, OA, osteoarthritis, and NA, not applicable. [a]Percentages are based on all pharmacological studies in the respective disease. [b]Percentages are based on all studies on biologic agents in the respective disease. [c]Multiple nominations per study possible. [d]E.g., no funding and conflicts of interest statement. [e]Median (IQR).

Table 2. *Proportions of elderly people in randomized controlled trials stratified by funding and intervention.*

	RA			OA		
Funding						
No industry funding	0.13	**0.17**	0.20	0.42	**0.47**	0.52
Any industry funding	0.14	**0.16**	0.18	0.33	**0.42**	0.50
Intervention						
Psychological	0.19	**0.29**	0.39	0.29	**0.50**	0.72
Surgical		**-**		0.40	**0.49**	0.58
Physical/physiotherapeutic	0.11	**0.18**	0.25	0.39	**0.46**	0.54
Pharmacological	0.14	**0.16**	0.18	0.36	**0.44**	0.53
Other	0.00	**0.09**	0.18	0.29	**0.39**	0.49

Numbers are the proportion of elderly people surrounded by 95% confidence intervals. RA, rheumatoid arthritis, and OA, osteoarthritis.

FIGURES

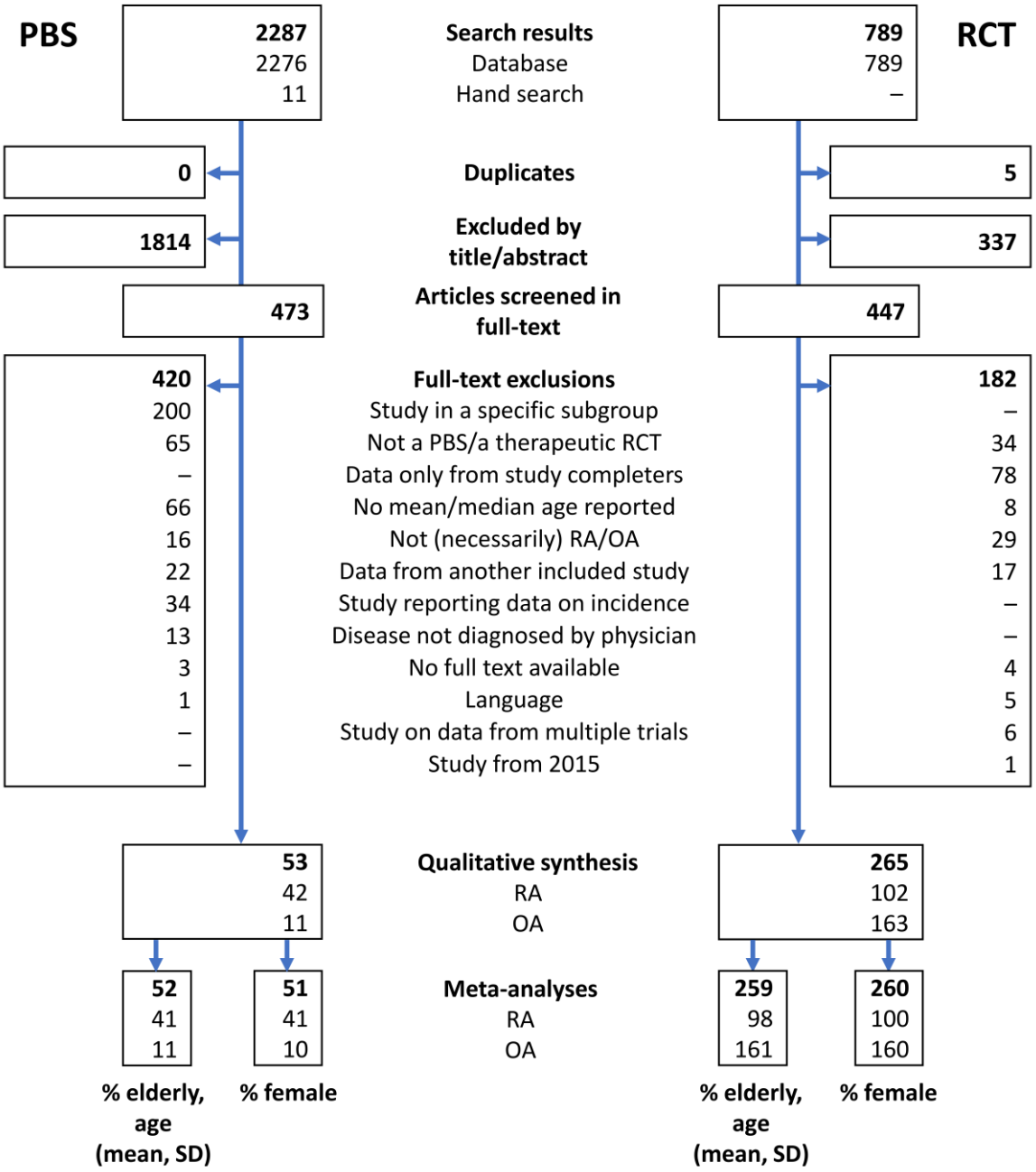

Figure 1. *Search flow of population-based studies (PBS) and randomized controlled trials (RCT) in rheumatoid arthritis (RA) and osteoarthritis (OA). Database searches were carried out on January 19, 2018.*

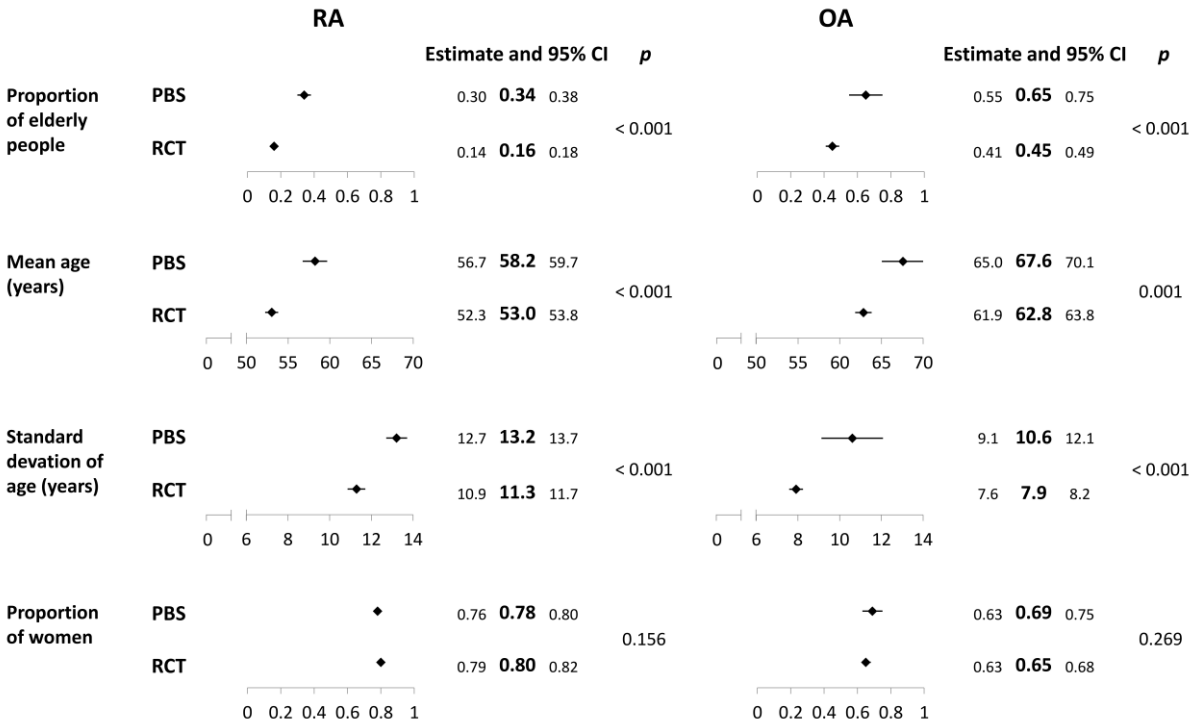

Figure 2. *Meta-analyses' estimates of population-based studies (PBS) and randomized controlled trials (RCT) in rheumatoid arthritis (RA) and osteoarthritis (OA) for the proportion of elderly people, mean age, standard deviation of age, and the proportion of women. CI, confidence interval.*