Sex Bias in Clinical Research: Representation of Women in Randomized Clinical Trials of major impact publications

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Estudi de recerca. Febrer de 2019

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Treball guanyador de l'accèssit de la branca de Ciències de la Salut del premi Clara Campoamor de la Unitat d'Igualtat de la Universitat de Barcelona al millor TFG amb perspectiva de gènere 2018-2019 i guanyador del primer premi al millor TFG amb perspectiva de gènere 2018-2019 de la Comissió d'Igualtat de la Facultat de Medicina i Ciències de la Salut de la Universitat de Barcelona.

Contextualització i Objectius: La recerca clínica històricament ha ignorat l'adequada representació de les dones i l'estudi de les diferències per sexe i per gènere. L'objectiu del present treball és examinar el fenomen del biaix de gènere en la medicina mitjançant la quantificació de la representació de les dones i l'anàlisi per sexe en els assajos clínics. Partim de la hipòtesi que dones i homes no es troben representats de forma equitativa en els estudis i que les dades no es reporten tenint en compte el sexe com a variable independent. **Mètodes:** Es localitzaren els assajos clínics aleatoris (ACAs) publicats durant 2017 en les tres principals revistes internacionals. S'exclogueren estudis on l'individu no constituïa la unitat d'anàlisi o que incloïen exclusivament un dels sexes. Es van recollir dades sobre el sexe dels participants en termes absoluts, el sexe de l'autor/a i la font de finançament. Així mateix, es va avaluar la correlació entre el fet de tenir una dona com a autora o un finançament públic i el percentatge de dones incloses. Així mateix, s'analitzà el compliment d'una *checklist* predefinida en l'avaluació de l'estudi del sexe o el gènere en el disseny de l'estudi. **Resultats:** Dels 333 ACAs obtinguts en la cerca, 150 foren seleccionats aleatòriament i 102 (68%) s'adheriren als criteris d'inclusió. El 79% (n=82) tenien un percentatge de dones del 30% o superior. Les dones constituïen el 42% de la població en global. Per als estudis del *NEJM*, aquest percentatge fou del 31%. Les dones com a autores o el finançament públic no es demostraren relacionats amb el percentatge de dones incloses excepte per la revista *Lancet* (P=0'04). Tan sols la meitat dels estudis consideraren el sexe en els mètodes (n=56, 57%) o reportaren resultats per sexe (n=50, 49%). **Conclusions:** Les troballes d'aquest estudi subratllen el fet que, tot i que la manca de representació de les dones s'ha reduït, encara existeix la necessitat de garantir l'anàlisi per sexe i les recomanacions específiques per sexe en els estudis clínics.

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"Quien está en posición de sujeto del discurso es el que mira y designa al otro. No se ve a si mismo como diferente, sino como norma canónica". Celia Amorós, Spanish philosopher, essayist and supporter of feminist theory.

"I am no longer accepting the things I cannot change. I am changing the things I cannot accept". Angela Davis, American political activist, academic, and former member of the Black Panthers Party.

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ABSTRACT. Background and Objectives: A proper representation of both women and the study of sex and gender differences had historically been overlooked in clinical research**.** The aim of this study is to examine the phenomenon of gender bias in medicine in terms of underrepresentation of women as well as underestimation of sex as a variable in reporting on clinical trials. We hypothesize that males and females are not included in equal numbers in trials, and that sex is not used as an independent variable when reporting data. **Methods:** Randomized Clinical Trials (RCTs) published in three prominent journals in 2017 were located by PubMed search. Studies where individuals were not the unit of analysis and those sex-specific were excluded. Data about participants' sex in absolute numbers, trial funding and sex of the authors was collected. In addition, we assessed whether studies with woman as authors and those publically funded were are as likely to include female participants as those with men. We also evaluated the compliance with a predefined checklist in terms of reporting of data and analysis by sex. **Results:** PubMed search located 333 RCTs. After a randomised sample selection of 150 studies and exclusion of ineligible articles, 102 (68%) remained for analysis. In 79% of the studies (n=82) women represented 30% of the study population or above. On average, 42% of trial's population were women. For *NEJM,* women represented only 31%. Female author or public funding were not correlated with the percentage of women enrolled except for *Lancet* (P=0'04). Only half of the studies considered sex on the methods (n=56, 57%) or reported results by sex (n=50, 49%). **Conclusions:** These findings underscore that although underrepresentation of women is being redressed, efforts are needed to ensure sex reporting and evidence based sex-specific recommendations.

BACKGROUND

Evidence based medicine is guided by results in randomized clinical trials (RCTs) which involve men and women as participants. The generalizability of clinical trials results relies on the conduct of clinical trials that have enough representation of both sexes. It's also evidence that many diseases place a heavier burden on women and may present with different signs and symptoms in this population group as is well described in cardiovascular disease (CVD) (1,2). In addition, it is well known that pharmacokinetics and pharmacodynamics differ between sexes, resulting in differential adverse event profiles with a further impact in treatment outcomes (3). Women are also major consumers of healthcare and prescription drugs, but studies prove that for the same health demand, the access to healthcare and new technologies is superior for men

(4,5). There are other variables that play a role, as could be social and cultural influences based on sex. One of them being differences between male and women in the approach with regard to their physicians and their own health (4,6,7) Therefore, sex may be a predictor not only of the incidence of disease, but also of the utility of diagnostic tests, preventive interventions, prognostic markers, and therapeutics (8). All this data underscores the importance of adequate representation of women in clinical trials population, which as evidence points out has not always been ensured (8–12).

Conceptualisation: Sex and Gender

Sex refers to a set of biological attributes associated with physical and physiological features including chromosomes, gene expression, hormone function and reproductive anatomy. Sex is usually categorized as female or male, although is known that there is a range of variation in the biological attributes that constitute sex and how they are expressed.

Gender designs the way in which society understands sex and there presupposes the existence of a gender order, so it affects how social determinants such as economic wealth, education, and political power are distributed between sexes due to a constantly ongoing social construction (5,13). Thus, sex and gender both impact environmental and occupational risks, risk-taking behaviours, access to health care, health-seeking behaviour, health care utilization and consequently disease prevalence and treatment outcome (2,4). In fact, gender perspective constitutes the analytic tool that ensures we are taking into account non-biological but also biological aspects in the interpretation of women's health (14). Hence, sex and gender are critical determinants of health and should be considered during the design of a study and so has been pointed out in major scientific journals (15–18).

Reasons for Not Studying Both Sexes

Ruiz and Vebrugge (19) presented a useful two-view model for understanding gender bias in the delivery of health services and research that was later actualised by Risberg et al. (14). One view assumes that health situations and risks are similar for women and men, when in fact they are not; while the other view assumes differences between sexes when there actually are similarities. These appears to be the origin of a biomedical model that assumes similarities in the case of physical health problems and differences when it comes to emotionally toned problems and self-expressed health.

Historical Perspective and Present Steps

The severe birth defects associated with thalidomide in the 1960s led to a conservative approach to testing of new drugs in women and in 1977, FDA issued a guideline which stated that "*women of childbearing potential* * *should be excluded from the earliest dose-ranging studies*". That exclusion inadvertently led to the underrepresentation or even exclusion of women from clinical trials. Because sex was not recognized as a variable in health research this exclusion was not questioned. Since the 1970s the scientific community has been warned that performing clinical trials on population consisting mostly of young middle-aged white man and generalizing the results to whole populations could lead to biased knowledge (20). Concern increased by the early 1980s, when the proportion of women in medical degrees reached 30% and women physicians began to reach a critical mass in academic medicine (21). This led to the US National Institutes of Health (NIH) issue of the *Revitalization Act* of 1993 and the FDA guidelines of 1994 (22). Both recommended that trials were "*designed and carried out in a manner sufficient to provide a valid analysis of whether the variables being studied in the trial affect women or minority groups (…) differently than other subjects in the trial*" (22). Since then the importance of examining differences in safety, efficacy, pharmacokinetics and pharmacodynamics among population subsets had been noted (13,15,16,18). Additionally, the Office of Research on Women's Health (ORWH) (25) was created to improve clinical study designs and procedures to better identify and evaluate possible sex differences in FDA regulated products. In Europe, clinical research was developed mostly in men until the 1990s. Afterwards, the International Conference on Harmonisation (ICH) promoted regulatory standards for clinical trials and issued several guidelines requiring a study population representative of the target patient population and analyses of the data with respect to sex (23).

Although this historical bias is being redressed through policies, it is restricted to recommendations and guidelines without specific legislation neither in the US nor in Europe. Specific strategies to implement guidelines for the study and evaluation of gender differences in the clinical evaluation of drugs have not been developed by the European Medicines Agency (EMA) since they don't agree with the ICH statements and consider guidelines specifically on women unnecessary, based on their international review and experience (24). This remaining bias leads to a prevailing underrepresentation of women in clinical research (8–12).

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* The term "child-bearing potential" was defined widely as any woman capable of becoming pregnant, including premenopausal single abstinent women, women using contraceptives, or women with sterile partners (30).

OBJECTIVES AND HYPOTHESES

The aim of this study is to examine the phenomenon of gender bias in medicine by analysing the inclusion of women and the reporting of data by sex in the RCTs published in main scientific journals. We hypothesize males and females are not included in clinical research in equal numbers and data is not reported or analysed using sex as an independent variable.

MATERIAL AND METHODS

Journal Selection

Journals were chosen focused in the areas of general and internal medicine, cardiac and CV systems, infectious diseases, emergency medicine and oncology (in which sex differences had been well documented previously) (1,4,8) and as seen on previous studies by Geller et al. (9,10) based on both their impact factor (IF) in 2016, as determined by Journal Citation Reports and by the number of publications in 2016. Only journals primarily publishing original clinical research were included. The three journals with major impact factor and more than 50 RCTs published in 2016 were selected.

Trial Selection

Trials were located by computerized search of PubMed using journal's ISSN to select all papers described as "Randomized Controlled Trial" that were based on data from humans and published during 2017. Sample-size calculation considered the need of 100 studies in order to have valid results, as seen elsewhere (9). We assumed a 30% of excluded studies, so a sample of 50 studies in each journal was selected by online randomisation. Inclusion criteria were population sample of 18 years or older and individuals as the unit of randomisation. If two studies analysed the same sample only the first was selected. Studies were excluded if sex-specific. Conditions that were not exclusive to one sex but may disproportionately affect members of one sex were not excluded.

Trial Examination

Each paper was examined entirely by a single reviewer including text, figures, tables and supplementary material. Information about corresponding author's sex, absolute number of men and women enrolled, topic of the study and funding source was collected. Sex of the author was determined by name's inspection or with Internet searching if ambiguous. Correlation between author's sex or funding source and sex distribution of participants was also assessed using the

Student t test. Significance was defined at the P=0.05 level. Papers were also evaluated to determine if sex was taken into account during the analysis of outcomes and if the authors acknowledged the impact that might have on either the results or their generalizability to broader populations. **Figure 1** provides a checklist with the items assessed for the gender analysis in each article section. All information was captured using a data collection form and entered into Microsoft Excel for analysis.

Title and Abstract	If only one sex is included in the study, or if the results of the study are to be applied to only one sex or gender, the title and the abstract specify the sex of human participants.
Introduction	Authors report, where relevant, whether sex and/or gender differences may be expected: - Research question(s) or hypotheses make reference to gender and/or sex - The influence of sex and gender factors are assessed a priori on the basis of their hypothesized role in the causation, course, treatment effectiveness, impact and outcome of health problems - Literature review cites prior studies that support the existence (or lack) of significant differences between women and men - Literature review points to the extent to which past research has taken gender or sex into account
Materials and Methods	Authors report how sex and gender are taken into account in the design of the study, whether they ensure adequate representation of males and females and justify the reasons for any exclusion, not only reporting number of males and females (stratification, subgroup analysis or inclusion of sex as a covariant in modelling). Flux diagram disaggregates data by sex.
Results	- Data is routinely presented disaggregated by sex and gender - Sex and gender-based analyses are reported regardless of positive or negative outcome - Data on withdrawals and dropouts are reported disaggregated by sex.
Discussion	- The potential implications of sex and gender on the study results and analyses are discussed. - If a sex and gender analysis is not conducted, the rationale is given. Authors further discuss the implications of the lack of such analysis on the interpretation of the results.

Figure 1: **Checklist used for RCTs examination.** Adapted from Heidari et al**.** (13)

RESULTS

The following journals met our criteria: *New England Journal of Medicine (NEJM), Lancet and Journal of the American Association (JAMA).* The search resulted in 333 publications; a sample of 150 trials was selected by randomisation. Of these, 48 were excluded. Reasons for exclusion can be seen in **Figure 2**. The remaining 102 studies (68%) were analysed.
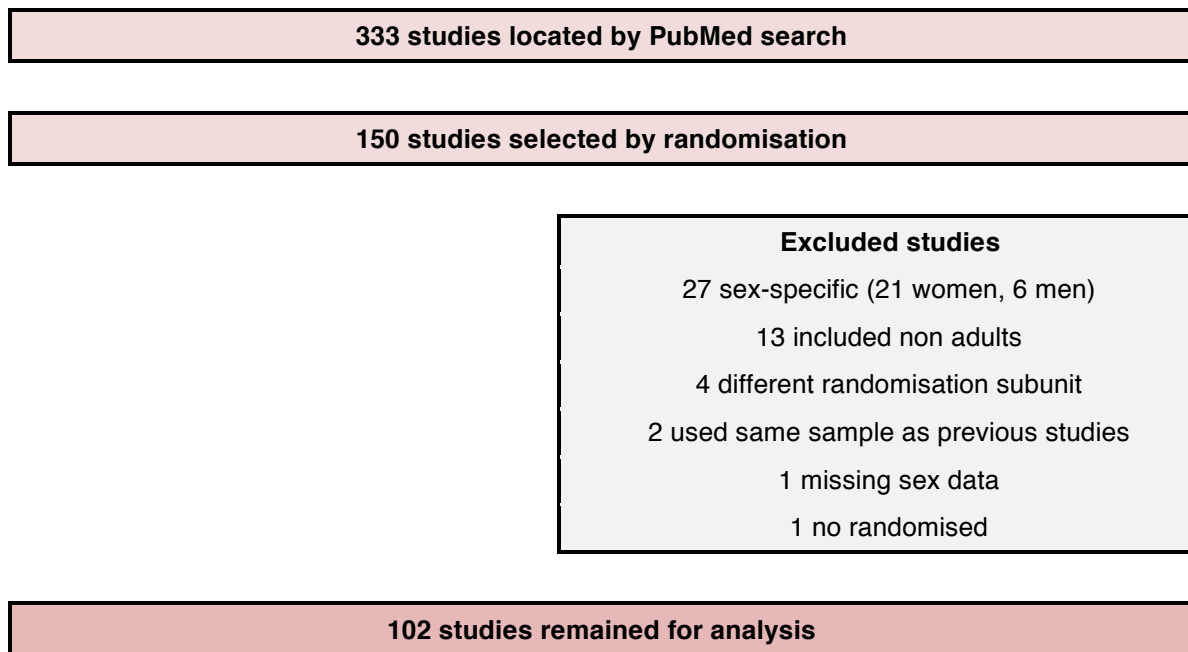
333 studies located by PubMed search

150 studies selected by randomisation

Excluded studies

27 sex-specific (21 women, 6 men)

13 included non adults

4 different randomisation subunit

2 used same sample as previous studies

1 missing sex data

1 no randomised

102 studies remained for analysis

Figure **2: Flowchart comprising included and excluded trials**

Sex Assessment

Globally, there were more men than women enrolled in RCTs (58% vs 42%). The percentage of women ranged from 40 to 50% In *Lancet* and *JAMA* (43% and 50% respectively) whereas for the *NEJM* women represented only 31%. The majority of studies (n=82, 79%) enrolled 30% or more women, except for 15 studies (20%), which included 20-29% women; and 5 studies (5%), which included <20% women. Of the studies enrolling less than 30% of women (n=20, 20%) only one acknowledged that the findings may not be applicable for women and emphasized the need for trials involving more females.

Individuals	*NEJM*	*Lancet*	*JAMA*	All studies
n	38	33	31	**102**
Total	135131	243547	22827	**401505**
Men	93063	121469	12917	**227449**
% Men	69%	50%	57%	**58%**
Median	2449	3681	417	**2182**
Women	42068	122078	9910	**174056**
% Women	31%	50%	43%	**42%**
Median	1107	3699	320	**1709**

Table 1: **Men and women enrolment in terms of absolute numbers, median and percentage in all studies and disaggregated by journal.** Based on data from *NEJM* (IF=72.406), *Lancet* (IF=42.831) and *JAMA* (IF=44.405).

The number of women enrolled ranged from 18 to 83334 (median 1079) whereas the number of men ranged from 16 to 86700 (median 2182). The percentage of both sexes ranged from 12% to 88%. **Table 1** and **Table 2** sum up data itemized by journal (supplementary data can be found on the **Appendix**).

Women enrolled (%)	*NEJM* (n=38)	*Lancet* (n=33)	*JAMA* (n=31)	All studies (n=102)
10-19%	1 (3)	2 (6)	2 (10)	5 (5)
20-29%	9 (24)	6 (18)	0	15 (15)
30-39%	11(29)	5 (15)	13 (42)	29 (28)
40-49%	6 (16)	7 (21)	10 (81)	23 (22)
50% or above	11 (29)	13 (39)	6 (19)	30 (29)

Table 2: **Percentage of women enrolled dissagregated by journal and in all studies: n (%).** Based on data from *NEJM* (IF=72.406), *Lancet* (IF=42.831) and *JAMA* (IF=44.405).

Author Sex

In all of the studies the sex of the main author was identified. Among these, the 82% (n=84) had a man as corresponding author. The journal with fewer women as authors was *NEJM*, with only a 13% (n=5). In studies with a woman as corresponding author females tend to be more represented and the sex representations appeared to be more balanced (51%) than when men was the corresponding author (40%). This finding was particularly evident for *NEJM* with 29% women enrolled with man as an author towards 56% women when a woman was the author. Although women as authors positively correlated with more women as participants (R^2=0'02), the correlation was weak and not statistically significant (P=0'09). Nevertheless, when looking individually on each journal, in *Lancet* female author appeared to be associated with larger percentage of women enrolled (P=0'04). Detailed statistical results can be found on the **Appendix**.

Trial Funding

Although there were no major differences in the percentage of women represented in public and privately funded trials (42% vs 36%), the percentage in publically funded ranged from 32% to 52%, whereas in privately funded studies ranged from 31% to 39%. The results were similar in all three journals (**Appendix**). Public funding was not found to be correlated to the percentage of

female participants (P=0.3) for all studies, but for studies in *Lancet* (P=0'03). Supplementary data is available on the ***Appendix***.

Phase III Trials

In all three journals, phase III studies represented more than 30% of the trials analysed. For phase III studies there were also overall more men (62%) than women enrolled, a consistent finding in all journals (***Appendix***).

Gender Analysis

A summary of the predefined checklist accomplishment can be found in ***Figure 5***. Only two publications (2%) reported whether sex or gender differences might be expected in the topic of the study. One of them expected sex differences in the main outcome and the other provided an explanation based on gender for women's expected outcome. Regarding methodology, half of the studies (n=57, 56%) took into account sex as a variable and/or included sex in the model. This was similar in all three journals (54%, 58% and 52% for *NEJM, Lancet* and *JAMA*, respectively). In six studies the analyses were not prespecified but post-hoc. Exclusively one of the RCTs, published in *Lancet,* had sex-specific intervention groups, which was also the only study that disaggregated the flux diagram by sex. In most of the studies (n=32, 56%) the evaluation was made in terms of subgroup analysis. Sex was included as a covariate in modelling in 20% of the studies (n=22) and stratification by sex in randomisation was made in three studies (3%).

Also half of the studies reported the analysis by sex in the results (n=50, 49%). In three studies data about withdrawals was provided segregated by sex. In six of the studies (6%) sex differences were found statistically significant. The 40% of phase III studies did not report sex information. Only three studies notified an insufficient sample for the analysis. According to adverse events reporting, only 5% differentiated results by sex and in two of the five studies the female specific reporting referred to pregnancy or breast cancer, which are conditions that exclusively or mostly affect women. In five (10%) of the studies that provided results by sex, the authors made a wrong use of the word gender when referring to sex. In the discussion, only nine studies (9%) provided information about the potential implications of sex and gender in the findings. In two of them the authors cited prior studies supporting the existence of differences in

outcomes between sexes. Only in two RCTs authors discuss the implication of sex imbalance on study sample.

		NEJM (n=38)	*Lancet* (n=33)	*JAMA* (n=31)	All studies (n=102)
Introduction		0	2 (6)	0	2 (2)
Methods	Analysis by sex provided or sex included in model	22 (54)	19 (58)	16 (52)	57 (56)
	Did not analyse by sex but provided explanation	0	0	2 (6)	2 (2)
	Did not include sex in analysis nor provide explanation	19 (46)	13 (40)	13 (41)	43 (42)
Results		19 (46)	19 (57)	12 (38)	50 (49)
Discussion		1 (2)	5 (15)	3 (10)	9 (9)

Table 3: **Checklist compliance on each section by journal and in all studies: n (%).** Based on data from *NEJM* (IF=72.406), *Lancet* (IF=42.831) and *JAMA* (IF=44.405).

DISCUSSION

Although the number of women participating in clinical trials has increased over the last two decades and the ORWH tracking data (25) based on studies publically funded shows a women enrolment of 50% or greater in the 2015-2016 period, women are still underrepresented in clinical trials in general. Overall, literature shows that women represent only 30-40% of patients enrolled in the clinical trials (8–11) and among trials recruiting both sexes, only one third report a gender-based analysis (8,9). Inclusion varies widely by indication and has been the lowest in cardiovascular trials. In fact, Scott et al. (26) reported in a 2018 review that the overall percentage of women participants was 34% and especially low enrolment (24%) was observed in ischemic heart disease and heart failure trials, the most common cardiovascular conditions affecting women.

Our findings are consistent with the available evidence. Among the 102 RCTs analysed, men represent the 60% and in median double women (2182 vs 1079 per study). One in four studies includes a percentage of women below 30%. Comparing the three journals analysed, the one with less women represented is *NEJM,* where men represented on average 70% of trial's population. Although underrepresentation of women should be seen as a study limitation, only one study acknowledged that the results might not be applicable to all populations due to the

lack of female individuals.

In respect to gender analysis, only 50% of the trials considered sex as a variable or included it as a covariant in the modelling. The reporting of analysis by sex on the results was mainly made in terms of subgroup analysis and in six of them the analysis was not prespecified but post-hoc. The lack of consistence between including sex in methods and reporting of the results is due to the fact that some studies, although they consider sex as a variable, fail to report the information of the findings if they appear to be negative, as it has been previously pointed out (15).

Only six studies found statistically significant different results by sex. Exclusively two studies reported expectable gender or sex differences in the introduction and only nine trials gave data on the discussion about the limitations of not including women or analysing data by sex or about the reasons for sex differences in the findings. This is specially concerning for phase III trials, which are supposed to include women in an amount suitable to allow valid subgroup analysis (23,27). The percentage of women involved was equivalent to the global (40%), but the 40% of the studies did not provide analysis by sex. In the same way, publically funded studies (42% of women enrolled) are those in which adherence to guidelines is expected (23,27), but only 48% (n=19) reported results by sex. Unlike previous studies (8), public source of funding was not correlated with a larger percentage of women enrolled (P=0'5) except for *Lancet* (P=0'03).

Despite this, failure to acknowledge the limitations of clinical research was frequent, with only two studies giving an explanation for underrepresentation of women or acknowledging that findings may not be generalizable to women, although reporting of limitations and generalizability of the results constitute items of the CONSORT guidelines for RCTs (28). Geller et al. (9) had suggested that the next CONSORT guidelines should include in these items to specifically comment on limitations and generalizability relative to the gender and ethnic/racial composition of the study participants. According to this line of thinking, guidelines for specific sex and gender reporting (13) had been developed recently (an example can be found on the **Appendix**). In fact, some journals as *JAMA* and *Nature* have instituted policies about reporting sex (17,18). Furthermore, databases that provide data by sex had been developed in order to encourage the investigators to make meta-analysis that cover this lack of knowledge (25).

All this data confirms that although the adequate representation of women in clinical trials is improving, it remains a lack of adherence to guidelines recommendations about reporting data by sex. This is specially concerning if we take into account that analysed journals are the ones with highest impact factor and so the role models to the rest, and that they had previously stated on their publications (15–18) the need of taking gender perspective into consideration. Even though the proportion of studies finding significant differences by sex was low (n=6, 5%), as patient complexity is very often underestimated in RCTs and the inclusion criteria might impose homogeneous clinical characteristics for men and women, studies can lack of sex differences in efficacy outcomes. In addition, although guidelines (23,27) require for phase III trials the determination of expectation of clinically important differences based on previous evidence in order to determine the need of subgroup analysis, if the evidence is lacking in reporting for sex differences in preliminary studies this becomes the basis for the failure to these analysis in subsequent research.

As a result, the inadequate participation of women in clinical trials can lead to several significant issues; including male-patterned inclusion criteria, sex-biased outcomes measurements and inadequate data analysis. Therefore, the evidence basis of medicine may be fundamentally flawed. The reporting bias that this methodology creates maintains a situation where guidelines based on the study of one sex may be generalized and applied to both and so the consequences translate into clinical outcomes. The CVD impact has been widely documented (1,2). Timely diagnosis of acute myocardial infarction (AMI) is often delayed in women because of their different symptom complex and the results of diagnostic testing for coronary artery disease can be falsely reassuring in women since the standard stress test has lower specificity and sensitivity (1). Furthermore, although pharmacokinetic and pharmacodynamic differences between sexes had been proved (3), there are many examples of drugs removed from the market in phase IV studies because of adverse events in women mostly because phase III trials are not powered to ascertain adverse events. An analysis of 10 prescription drugs that were withdrawn in the market from 1997-2001 found that 8 posed greater health risks for women. (29) Similar to these data, only 5% of the studies analysed differentiated results by sex and in two of the five studies it referred to conditions that exclusively or mostly affect women. Sex and gender-based analysis would have provided sufficient information to guide dosing and applicability prior to approval.

According to that, we can talk about a remaining gender bias in clinical trials. The term bias refers to the existence of a systematic error that leads to wrong results. Underrepresentation of women goes along with a clinical practice that underestimates women's health issues, considering them variations of the norm, the norm being men's expression of pathology. Available evidence (2,4), as it has been assessed on the background, describes differential health value attending to sex of the patient. An example of this is the definition of "Atypical AMI symptoms" referring to those more prevalent in women opposing it to the canonical presentation of AMI, which is the one derived from trials and so more prevalent in men (1,2). As a result, gender bias can be considered a way of systematic error in evidence-based medicine. In literature (14,19), the term preferred is *gender bias* and not *sex bias*[†] because it is the gender order, previously approached, what provides an explanation to underrepresentation and undervaluation of women's health. Actually, gender studies (6) had suggested hypothesis for the less participation of women in clinical trials or women's withdrawals such as caretaking roles and low socioeconomic status. Even so, reasons for withdrawal are not usually reported and in our case only in three studies data about baseline characteristics of these populations was given.

Gender blindness and stereotyped preconceptions about men and women are identified as key causes to gender bias (14). Men had been the main knowledge producers and in fact, they still hold the majority of trial's authorship, as data on this study (88% of authors were men) and previous evidence (21) support, so it has been suggested that the male perspective could be one of the reasons that lead to bias. Despite this, we didn't find that trials with women as authors were more like to include women (P=0'09) except for *Lancet* studies subgroup (P=0'04) although it has been described on previous studies (8) and maybe because the small size of the sample (n=18).

The information disaggregated by sex tells us whether differences by sex exist in some specific dimension of health, but the information by gender sensitivity is constructed to help arise the reasons and consequences of these. Nowadays the analysis is restricted to sex reporting in the results and so the use of the term gender is frequently mixed up. In fact, in 5% of the studies analysed the term gender was misused when referring to sex. Consequently, it appears that

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[†] In the present study we talk about *sex bias* because we focus on proportion of female participants, biological differences and sex-specific reporting.

several of the guidelines include gender issues in their protocols although these recommendations are not reinforced, as it is not usual that reports of clinical trials include the minimum gender information (8,9). When researchers do find subgroup differences, they frequently fail to distinguish between biological and social causes of difference, portraying differences as biologically inevitable and drawing attention away from the social constructs that cause observed health disparities (9). Ensuring adequate women's representation in clinical trials constitutes the first step in the building of an egalitarian medicine that takes into account gender on its practice. Freedman et al. (30) describe an ideal progression in research, where potential differences among sex groups found as a result of subgroup analysis lead to studies where the primary question is asked separately for each group, and the resulting study is designed with separate groups in mind. Consequently, analysis and interpretation of differences between subgroups should move forward to a combined approach that considers biological as well as non-biological explanations, interrelating other factors that contribute to generate health inequalities and which have also been undervalued in clinical trials, as are gender, race and class (7,10). Therefore, differences in health outcomes in individuals should be assessed under and intersectional view.

The present study contributes to the existing evidence rising awareness towards the need to achieve an adequate representation of women in clinical trials and ensure sex reporting of the results. The purpose of these should be the building of solid knowledge that takes into account biological and non-biological aspects in order to warrant the best approach to patients. Evidence-based medicine, when it adheres to scientific methods, is the only way to provide high quality knowledge that closest reflects reality, as it states that clinical practice should be based on rigorous scientific studies and not in perpetrated historical routines lacking of scientific support. Similarly, and as Ruiz-Cantero et al. (4) point out, feminist epistemology considers androcentricity and sexism forms of social bias that can be addressed through strict adhesion to scientific method.

Limitations of this study

Because only RCTs were included on the analysis, data about cohort studies and meta-analysis were not taken into consideration, although they might include a higher women proportion as they have broad inclusion criteria. Nevertheless, the aim of the study was to determine women representation in highest level of evidence literature, as those are the studies with greater

impact on clinical practice. Moreover, no comparison between the proportion of women in RCTs and the proportion of women among the population with a given disease has been carried out. Despite this, the estimation of adequate representation of women in trials is highly dependent on reliable measures of disease prevalence and obtaining such estimates can be fraught with detection bias and variations with regard to case definition. In addition, guidelines point out that women should be represented in percentages similar to men regardless of disease prevalence. The fact that the analysis was limited to which was reported on paper or supplementary material might have implied missing of other information. Last, as only a reviewer examined the papers this might have led to mistakes that could have been reduced with a second inspection.

CONCLUSIONS

- Gender bias represents a current deal in evidence-based medicine, since differences in the way in which pathologies affect women had not always been assessed.
- In a selected sample of original articles published in top biomedical journals, women are represented nearly equal as men in most of the cases and so historical underrepresentation of women in trials is being redressed.
- Only half of randomised clinical trials report data by sex and so efforts are still needed to ensure inclusion of sex as a variable in the design of clinical trials.
- Steps in order to settle gender bias should have the goal of building a gender sensitive medicine that takes into account biological and non biological aspects

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Appendix

ABBREVIATIONS

AMI: Acute Myocardial Infarction

CVD: Cardiovascular Disease

EMA: European Medicines Agency

FDA: Food and Drug Administration

ICH: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

IF: Impact Factor

JAMA: *Journal of the American Medical Association*

NEJM: *New England Journal of Medicine*

NIH: National Institutes of Health

ORWH: Office on Research on Women's Health

RCTs: Randomized Clinical Trials

SUPPLEMENTARY TABLES

Table 1. **Men and women enrolment in terms of absolute numbers, median and percentage in all studies and disaggregated by journal for trials with a man as corresponding author (A) and a woman as corresponding author (B).**

Based on data from *NEJM* (IF=72.406), *Lancet* (IF=42.831) and *JAMA* (IF=44.405).

A

Man author	*NEJM*	*Lancet*	*JAMA*	All studies
n	33	28	23	84
%	87%	85%	74%	82%
Total	123875	71875	12173	207923
Men	88163	37396	7024	132583
% Men	71%	52%	58%	60%
Median	2672	1336	305	1437
Women	35712	34479	5149	75340
% Women	29%	48%	42%	40%
Median	1082	1231	224	846

B

Women author	*NEJM*	*Lancet*	*JAMA*	All studies
n	5	5	8	18
%	13%	15%	26%	18%
Total	11256	171380	105654	288290
Men	4900	83937	5893	94730
% Men	44%	49%	55%	49%
Median	980	16787	737	6168
Women	6356	87443	4761	98560
% Women	56%	51%	45%	51%
Median	1271	17489	595	6452

Table 2. **Men and women enrolment in terms of absolute numbers, median and percentage in all studies and disaggregated by journal for publically funded trials (A) and privately funded trials (B).**

Based on data from *NEJM* (IF=72.406), *Lancet* (IF=42.831) and *JAMA* (IF=44.405).

A

Public	*NEJM*	*Lancet*	*JAMA*	All studies
n	4	15	21	40
%	11%	45%	68%	41%
Total	1714	230861	16899	249474
Men	1172	113597	9309	124078
% Men	68%	49%	55%	58%
Median	293	7573	443	2770
Women	542	117264	7590	125396
% Women	32%	51%	45%	42%
Median	5149	7818	361	4443

B

Private	*NEJM*	*Lancet*	*JAMA*	All studies
n	34	18	10	62
%	89%	55%	32%	59%
Total	133417	12686	5928	152031
Men	91891	7872	3608	103371
% Men	69%	62%	61%	64%
Median	2703	437	361	1167
Women	41526	4814	2320	48660
% Women	31%	38%	39%	36%
Median	1221	267	232	574

***Table 3*. Men and women enrolment in terms of absolute numbers, median and percentage in Phase III studies.**

Based on data from *NEJM* (IF=72.406), *Lancet* (IF=42.831) and *JAMA* (IF=44.405).

Phase III	*NEJM*	*Lancet*	*JAMA*	All studies
n	25	15	10	**50**
%	66%	45%	32%	**48%**
Total	116873	11277	6274	**134424**
Men	81030	6734	3502	**91266**
% Men	69%	60%	56%	**62%**
Median	3241	449	350	**1347**
Women	35843	4543	2772	**43158**
% Women	31%	40%	44%	**38%**
Median	1434	303	277	**671**

***Table 4*. Results on Student t test for the correlation between women as author and percentage of women involved in all studies (A) and each journal separately: *NEJM* (B), *Lancet* (C) and *JAMA* (D).**

Based on data from *NEJM* (IF=72.406), *Lancet* (IF=42.831) and *JAMA* (IF=44.405).

A

Adjusted R^2 value	0.018090358
P-value	0.0938773

B

Adjusted R^2 value	-0.015128378
P-value	0.507277903

C

Adjusted R^2 value	0.120062677
P-value	0.048220189

D

Adjusted R^2 value	-0.030592593
P-value	0.743131694

Table 5. **Results on Student t test for the correlation between women as author and percentage of women involved in all studies (A) and each journal separately: *NEJM* (B), *Lancet* (C) and *JAMA* (D).**

Based on data from *NEJM* (IF=72.406), *Lancet* (IF=42.831) and *JAMA* (IF=44.405).

A

Adjusted R^2 value	0.000668671
P-value	0.303984832

B

Adjusted R^2 value	-0.022383928
P-value	0.665579321

C

Adjusted R^2 value	0.101467358
P-value	0.039646047

D

Adjusted R^2 value	-0.032963493
P-value	0.837823771

SUPPLEMENTARY FIGURES

Figure 1. **Authors' checklist for gender-sensitive reporting.**

Source: Sex and Gender Equity in Research (SAGER) Guidelines (13).

Research approaches ✓

  ✓ Are the concepts of gender and/or sex used in your research project?

  ✓ If yes, have you explicitly defined the concepts of gender and/or sex? Is it clear what aspects of gender and/or sex are being examined in your study?

  ✓ If no, do you consider this to be a significant limitation? Given existing knowledge in the relevant literature, are there plausible gender and/or sex factors that should have been considered? If you consider sex and/or gender to be highly relevant to your proposed research, the research design should reflect this

Research questions and hypotheses

  ✓ Does your research question(s) or hypothesis/es make reference to gender and/or sex, or relevant groups or phenomena? (e.g., differences between males and females, differences among women, seeking to understand a gendered phenomenon such as masculinity)

Literature review

  ✓ Does your literature review cite prior studies that support the existence (or lack) of significant differences between women and men, boys and girls, or males and females?

  ✓ Does your literature review point to the extent to which past research has taken gender or sex into account?

Research methods

  ✓ Is your sample appropriate to capture gender and/or sex-based factors?

  ✓ Is it possible to collect data that are disaggregated by sex and/or gender?

  ✓ Are the inclusion and exclusion criteria well justified with respect to sex and/or gender? (Note: this pertains to human and animal subjects and biological systems that are not whole organisms)

  ✓ Is the data collection method proposed in your study appropriate for investigation of sex and/or gender?

  ✓ Is your analytic approach appropriate and rigorous enough to capture gender and/or sex-based factors?

Ethics

  ✓ Does your study design account for the relevant ethical issues that might have particular significance with respect to gender and/or sex? (e.g., inclusion of pregnant women in clinical trials)

Consideracions sobre el treball

AUTOAVALUACIÓ

Aquest Treball de Fi de Grau és el resultat d'una recerca bibliogràfica i anàlisi de dades sistemàtica i exhaustiva que he dut a terme jo mateixa, així com l'anàlisi estadística i l'elaboració de taules i figures. La feina sobre totes aquestes dades cristal·litza en una discussió també elaborada personalment. En tot aquest procés he disposat de l'assessorament del meu tutor, que ha contribuït a l'hora de redirigir el treball per garantir-ne una millor qualitat científica.

L'elaboració del present treball, amb les seves limitacions, m'ha permès profunditzar sobre un tema rarament tractat en l'acadèmia, com és la vigència d'errors metodològics en el desenvolupament dels estudis que generen l'evidència científica en la que es basa la pràctica mèdica. El treball neix de la necessitat de reavaluar la històrica infrarrepresentació de les dones en els estudis clínics i la manca d'anàlisi de les dades per sexe i/o gènere. Això implica un qüestionament de les premisses de la medicina basada en l'evidència, font de coneixement en la nostra professió. Aquest fenomen, tot i afectar directament la salut de les dones, no és abordat durant la carrera i doncs contribueix a perpetuar la situació d'inferioritat i de distribució desigual dels recursos entre dones i homes. La idea de realitzar aquesta recerca fou per tant original i inspirada en lectures extracurriculars. Els resultats presentats ofereixen una nova mirada sobre la recerca i ens plantegen la necessitat permanent de dubtar davant el que està establert com a canònic. A més, proporciona la base per avançar cap a un model de medicina individualitzada, entenent aquesta com la que contempla el context i la realitat material dels pacients a l'hora d'abordar les patologies. Un model de medicina que cal promoure des de les universitats i que, d'acord amb el que estableix l'*Agència per a la Qualitat del Sistema Universitari de Catalunya*[‡]*,* ha d'incorporar la perspectiva de gènere a tots els nivells: docència, recerca i pràctica clínica.

[‡] Agència de Qualitat del Sistema Universitari de Catalunya. Generació de coneixement. Disponible a: http://www.aqu.cat/aqu/actualitat/noticies/39617587.html#.XEiDuPzZBnb