Doubly blind: a systematic review of gender in randomised controlled trials

Susan P. Phillips¹,²* and Katarina Hamberg³

¹Departments of Family Medicine and Public Health Sciences, Queen’s University, Kingston, Canada; ²Umeå Centre for Gender Studies, Umeå University, Umeå, Sweden; ³Department of Public Health and Clinical Medicine, Family Medicine, Umeå University, Umeå, Sweden

Background: Although observational data show social characteristics such as gender or socio-economic status to be strong predictors of health, their impact is seldom investigated in randomised controlled studies (RCTs).

Objective & design: Using a random sample of recent RCTs from high-impact journals, we examined how the most often recorded social characteristic, sex/gender, is considered in design, analysis, and interpretation. Of 712 RCTs published from September 2008 to 31 December 2013 in the Annals of Internal Medicine, British Medical Journal, Lancet, Canadian Medical Association Journal, or New England Journal of Medicine, we randomly selected 57 to analyse funding, methods, number of centres, documentation of social circumstances, inclusion/exclusion criteria, proportions of women/men, and reporting about sex/gender in analyses and discussion.

Results: Participants’ sex was recorded in most studies (52/57). Thirty-nine percent included men and women approximately equally. Overrepresentation of men in 43% of studies without explicit exclusions for women suggested interference in selection processes. The minority of studies that did analyse sex/gender differences (22%) did not discuss or reflect upon these, or dismissed significant findings. Two studies reinforced traditional beliefs about women’s roles, finding no impact of breastfeeding on infant health but nevertheless reporting possible benefits. Questionable methods such as changing protocols mid-study, having undefined exclusion criteria, allowing local researchers to remove participants from studies, and suggesting possible benefit where none was found were evident, particularly in industry-funded research.

Conclusions: Social characteristics like sex/gender remain hidden from analyses and interpretation in RCTs, with loss of information and embedding of error all along the path from design to interpretation, and therefore, to uptake in clinical practice. Our results suggest that to broaden external validity, in particular, more refined trial designs and analyses that account for sex/gender and other social characteristics are needed.

Keywords: clinical trials; randomised controlled trial; gender; socio-economic status; social determinants; social epidemiology; sex differences

Responsible Editor: Malin Eriksson, Epidemiology and Global Health, Umeå University, Sweden.

*Correspondence to: Susan P. Phillips, Department of Family Medicine, Queen’s University, 220 Bagot St., Kingston K7L 5E9, Canada, Email: phillip@queensu.ca

Received: 1 September 2015; Revised: 25 January 2016; Accepted: 21 February 2016; Published: 15 April 2016
eliminated as sources of bias, while researchers manipulate or control exposures of interest. The weakness is that unless they are managed as variables for analysis the very real impact of those social circumstances on the study endpoint, and interactions with the intervention of interest are hidden. Resulting study findings will then speak only of efficacy in a population cleansed of personal traits and social circumstances, but not of effectiveness and external validity in the real world where no one is devoid of such characteristics as sex/gender or SES.

Lifetime fluctuations in and the social nature of circumstances like SES are readily apparent; however, placing sex and gender among these may require explanation. Sex and gender are two separate but intertwined terms used for categorisation and analyses of men and women. Sex refers to biological attributes and is primarily associated with physical and physiological features, including chromosomes, hormone function, and sexual anatomy. Gender goes beyond biology and refers to the socially constructed roles, behaviours, expressions, and identities of girls, women, boys, men, and gender diverse people. It influences how people perceive themselves and each other, how they act and interact, and the distribution of power and resources in society. Gender is not static and not something a person possesses, it is rather an activity. The concept of ‘doing gender’ manifests this. Doing gender most often incorporates, but can also challenge explicit and implicit social norms, constraints, and expectations that alter ways of behaving and acting as men and women (3–5). Like SES, gender will vary across settings and over time. Although the impact of a group or society’s gender norms is not ubiquitous or homogeneous, there are commonalities arising from the experience of being, for example, a woman within a given grouping. Furthermore, like SES, gender can, although it does not always, affect health and wellbeing. For example, in many cultures girls are undervalued relative to boys and are therefore fed less. Similarly, women in many countries are less educated than men, not because of limited individual capacity but because societal and cultural norms imply that higher education is only for men. In countries where women are well educated, or even more educated than men, they are still often under-represented in high-ranked and well-paid jobs, suggesting that gender inequality is not restricted to developing countries but is a worldwide phenomenon. Women currently outlive men globally; however, their longevity advantage has and continues to fluctuate with time and social circumstances (6). This life expectancy difference likely arises from how men and women live their lives, which work and activities they engage in, and risks they are exposed to or take (7–9). Changes in other social circumstances may change the expectations of and roles consigned to men or to women and may accordingly change their doing of gender, illustrating that gender is not a fixed characteristic (5).

In reality, it is seldom possible to isolate sex from gender, as biology interacts with social and environmental living conditions, and sex and gender become tangled together. Genes can be activated or shut down (temporarily or permanently) by environmental factors and ways of living. Since men and women often live different lives with different duties, demands, and resources, this newer epigenetic knowledge contributes to insights about how gender and sex are intertwined. Therefore, using the terms sex and gender has to be done with caution. In this article, we use the term ‘sex-specific’ when talking about diseases or conditions that are restricted to either men or women, like prostate cancer or preterm birth. Gender is used as a separate term when we talk about bias related to being either women or men – because the creation of gender bias is by definition a social process whereby preconceptions and ideas about women and men skew research, investigations, or treatment. Sex or gender are also used as separate terms as the authors of a specific reviewed paper did so. However, we prefer sex/gender as a term that recognises that biology shapes social context which, in turn, shapes biology.

Within a randomly selected sample, exposures being examined may not have uniform or homogeneous effects across social groupings such as sex/gender, race or SES, of study participants (10). If variability is not individual but instead arises from a characteristic of a social subgroup, the statistical independence of participants will be jeopardised. Failure to recognise that subjects may not be independent will introduce error despite randomisation (10). Observational research has demonstrated strong and extensive health effects arising from and associated with membership in the groupings, ‘women’ and ‘men’. Significant sex/gender differences have been well documented with respect to, for example, heart diseases (11) and type 2 diabetes (12). Pharmacokinetics may differ for men and women, as can benefits, side effects, and adverse reactions to drugs (13). Unequal access to medical care for women and men in many settings is of importance in understanding treatment and health outcomes. Finally, gender bias has been demonstrated in clinical decision-making (14, 15). Although it does not always alter health, evidence is strong enough to justify considering sex/gender whenever possible, as a modifier of the relationship between intervention and medical outcome (16).

To directly study the impact of any characteristics on a particular outcome in experimental designs requires the ability to randomly allocate these to participants. Although not fixed, social characteristics cannot be randomly assigned. Nevertheless, it is possible to estimate how traits like sex/gender or SES alter outcomes rather than dismissing them as topics not worthy of study in a particular trial. At a minimum, examining interactions of these with independent variables will hint at their effect. Powering a study to enable a priori randomisation of
recruited women and men separately so that the study intervention can be examined both within and across these groupings and to assess interactions of social determinants with other variables will increase accuracy and meaning (17–19).

The aim of this systematic sampling review of recent randomised controlled studies (RCTs) is to determine whether and how the social traits of sex/gender are addressed in design, analysis, and interpretation of study findings and to then consider the meanings and impact of the methodologies used. We selected sex/gender for specific examination because the categories ‘man’ and ‘woman’ were the most commonly identified social characteristics in the reviewed RCTs.

Methods

Sample selection
In September 2013, we searched PubMed using the terms randomised controlled trial, clinical trial, human, Annals of Internal Medicine, British Medical Journal, Lancet, Canadian Medical Association Journal, New England Journal of Medicine and the search filters clinical trial, September 2008–1 July 2013. We then sorted the initial 588 papers retrieved by date of publication to randomise papers from each journal and ensure sampling of the entire time frame, and selected every 20th paper for inclusion. In January 2014, a similar search with date limits of July 2013 to 31 December 2013 yielded another 124 papers, of which every fourth paper was selected for review. Recent papers were oversampled to ensure that findings reflected most current research methodology.

When a selected paper was not an RCT (n = 6), the next paper on the list was substituted. To establish our analytical method and construct a data extraction template, five studies were reviewed by both researchers, then three more were reviewed independently, and thereafter discussed for concordance of data extraction. After each reviewing another 10 and 9 studies, respectively, both authors again checked for inter-reviewer consistency in approach, information extraction, and interpretation of findings, then reviewed 30 more papers (15 each) independently. All in all, 57 papers were included in the analysis. Sample selection is summarised in Fig. 1.

Data extracted and analysis
Although many authors in the sample used the concepts ‘sex’ and ‘gender’ as interchangeable synonyms and without defining them when describing inclusion, exclusion, or effects of being men or women, we used the combined term sex/gender in our data extraction templates. Authors generally documented body mass index (BMI) only in studies of diseases where weight was an important factor in a biological sense. However, as BMI is also strongly related

Fig. 1. Flow diagram of study search, randomisation, and selection.
to and entangled with the level of education, family economy, and other aspects of SES, we included it as a social factor when extracting data. We noted inclusion/exclusion criteria for each social category (sex/gender, race, SES, social connectedness, health behaviours, education, BMI). After identifying that sex/gender was the most commonly recorded of these social categories, we focused further analyses on how sex/gender was or was not addressed in research design, analysis, and interpretation. To do this, we re-read and re-extracted the following data from all papers: inclusion/exclusion criteria, whether the study topic was sex-specific, number and proportion of women and men in the study, and how sex/gender was addressed and reported in results and discussion. A narrative summary of methodological strengths and shortcomings overall was also documented for each study.

Results

The 57 trials reviewed are summarised in Table 1 (20–76). In total, six papers reported on sex-specific conditions (36, 47, 48, 58, 68, 74). Table 2 identifies social characteristics documented across the reviewed papers. Most frequently recorded was sex/gender (52/57, 91%), followed by race or ethnicity (30/57, 53%), or some aspect of SES (9/57, 16%). Although BMI, a possible proxy for SES, was sometimes recorded its use was solely as a physical indicator of risk. Social connectedness and past or present adversity, both known determinants of health, were not documented in the reviewed trials. Thirty-five studies (61%) had age-related exclusions, few of which were necessary given the condition being assessed. One trial excluded women without explanation. In this study of diabetes, subjects recruited through primary care practices were all men (39). Conversely, in what was designed as a sex-specific study of the impact of peer support for mothers on maternal and child morbidity and mortality in Malawi, researchers allowed men to participate in women’s support groups (47). Pregnant women, or those who might become pregnant, were excluded in 13 of the 54 studies (24%) of either women alone or both men and women.

Table 3 documents whether and how sex/gender was addressed in the studies reviewed. We considered papers where women and men were included in proportions ranging from 40 to 60% as having equal representation. Of the 51 non-sex-specific trials, 20 (39%) enrolled women and men in roughly equal proportions, 22 (43%) included more than 60% men, in 5 (10%) more than 60% of participants were women, and sex/gender proportions were not documented in three studies conducted among adults and two among children. Not noted in Table 3 is that the majority of papers in the sample used the concepts ‘sex’ and ‘gender’ as undefined synonyms when describing inclusions, exclusions, results, and in discussions.

Explicit and implicit methodological aberrations were not uncommon (see Table 1) particularly with respect to selection of participants. In five papers, for example, there were unclear reasons for exclusions or high numbers of unexplained dropouts among those already enrolled (24, 30, 44, 52, 55). In a different study, 371 (~25%) of those randomised to the treatment group yet none in the control group were unavailable to consent and were therefore excluded (53). In another study almost 80% of recruits were removed (44). We noted that arbitrary and ill-defined options to exclude participants at intake or after were more common in trials with some or all funding from industry (90%) (24, 30, 39, 52–55, 60, 73) than solely from public sources (44). For five of the eight trials that were not blinded, there was no reason related to the intervention itself that would preclude this standard methodology (48, 53, 56, 59, 75).

Next we examined whether and how sex/gender differences were analysed and included in results. Of the 49 of 51 studies on non-sex-specific conditions that included both women and men, only 10 (20%) used these categories to differentiate findings either via disaggregating data (n = 8) (20, 34, 63, 67, 69–72) and/or by examining interactions between sex/gender and other variables of interest (n = 3) (26, 63, 70).

Aspects of sex/gender that were described in outcomes were sometimes discussed (20, 51, 57, 63, 67, 71). Also, in one of the six studies of sex-specific conditions there was discussion of whether gender aspects like social roles, opportunities, constraints, and expectations inherent in being a woman might interact with findings (48). Conversely, identified differences between women and men were, on occasion, not reported in results but alluded to in subsequent discussions (48, 60) or in appendices (54). Overall, the interactions between sex/gender and other social determinants of health (e.g. SES, education, race) that would enrich understanding were neither included nor discussed as missing explanatory indicators, possible sources of error, or as predictors of the outcome.

Discussion

In this systematic sampling review of recent RCTs, we have assessed whether social traits exemplified by sex/gender were included in or potentially biased findings. Studies continue to show that women are underrepresented in enrolment (77, 78) in National Institutes of Health (NIH) funded clinical research despite funding guidelines (79–81) in research on specific diseases (82–84), in analyses (85), and when mortality is an endpoint (86). Our question went beyond inclusion of women to examine whether and how the impact of diversity in baseline social characteristics within study arms was addressed. We selected sex/gender for in-depth examination recognising that inclusion is a prerequisite for but does not alone address the social character of being men and women. It is because dissimilar characteristics of subgroups such as men and women can and do modify outcomes and should be addressed that major
| Author, Funding (public, industry, both), (reference number) | Aim/Question | Outcome | Population characteristics number, sex, race/ethnicity, age, measure of SES | Additional notes on method |
|-----------------------------------------------------------|-------------|---------|------------------------------------------------------------------------|---------------------------|
| Aberele (industry) (20) | Comparison of low dose CT and x-ray screening for detection and survival of lung cancer | Earlier detection with CT but also more false positives Decrease in the number of advanced-stage cancers detected | N > 53,000 Women = 39% Documented race, marital status, education, BMI, workplace risk | Compared participants to overall population to show external validity |
| Anderson (public) (21) | Comparison of Dalteparin versus ASA for extended DVT prophylaxis after hip arthroplasty | ASA was equally beneficial and much less costly | N = 785 Women = 43% Documented BMI, smoking | Reported as non-inferior |
| Boyd (primarily industry) (22) | Comparison of two drug regimens for HIV after failure of first-line treatment | Found no benefit to new treatment | N = 558 Women = 47% Age > 16 Documented ethnicity, sexual orientation | Reported as non-inferior |
| Burmester (industry) (23) | Comparison of methotrexate or tofacitinib for second-line treatment of RA | Combination treatment was effective | N = 399 Women = 84% Documented race | Phase 3 drug trial |
| Byrd (industry) (24) | Comparison of two doses of a drug to treat CLL | Outcome described drug as effective but without a control group | N = 85 Women = 24% | Protocol changed during study Preponderance of men 34% attrition from study – unclear if they dropped out or were removed or whether they were included in analyses Endpoints unclear |
| Chakravarthy (public) (25) | A comparison of two drugs to treat macular degeneration | Outcomes were similar for each group but one drug was less costly | N = 628 Women = 60% Age > 50 Documented quality of life, depression | Unclear why study included depression as an independent variable |
| Cooper (public/industry) (26) | Comparision of medication alone or with stenting for renal artery stenosis and hypertension or chronic renal disease | No difference in outcomes | N = 931 Women = 50% Age 18+ Documented quality of life, depression | Pre-specified secondary analyses of interactions with sex, race, and medical variables |
| Cotton (public/industry provided drugs) (27) | Comparison of early versus deferred anti-retrovirals for infants with HIV | Early treatment improved long-term outcomes | N = 377 Sex not specified Age > 12 weeks Documented race, BMI, smoking | Could have compared boys and girls to assess differences in immune response |
| Dennis (public/industry) (28) | Does intermittent pressure reduce DVT risk days to weeks post-stroke better than no treatment? | Absolute risk reduction 3.6% with more skin problems in treatment group | N = 2,876 Women ~ 50% Documented ‘overweight’ and ‘lives alone’ | Not blinded |
| Author, Funding (public, industry, both), (reference number) | Aim/Question | Outcome | Population characteristics, sex, race/ethnicity, age, measure of SES | Additional notes on method |
|------------------------------------------------------------|-------------|---------|--------------------------------------------------------------------|---------------------------|
| Devanand (public) (29) | Does stopping risperidone precipitate psychosis among Alzheimer’s patients? | Increased psychosis when drug stopped | N = 110  
Women — 60%  
Age 50–90  
Documented race, place of residence |  |
| Doody (industry) (30) | Comparison of drug versus no treatment for Alzheimer’s disease | Treatment group had worse outcomes and more side effects | N = 1,537  
Women — 54%  
Age < 55  
Documented race, place of residence | Phase 3 drug trial  
Many (~ 1/3) subjects removed from study despite meeting inclusion criteria |
| Dooley (industry) (31) | Comparison of mycophenolate versus azathioprine for lupus-induced renal failure | Mycophenolate significantly better for all outcomes | N = 227  
Women — 86%  
Age 12–75  
Documented weight, urban/rural residence | 45% withdrawal secondary to side effects (sex undisclosed) |
| Douillard (industry) (32) | Comparison of new and conventional treatments for colorectal cancer based on genetic markers | Outcomes were associated with presence of gene mutations | N = 620  
Women — 30%  
Age 18+  
Documented race, ethnicity |  |
| Elkenboom (industry) (33) | Comparison of dabigatran and warfarin in patients with mechanical heart valves | Excess thrombolysis and bleeding in dabigatran group such that study was terminated | N = 252  
Women — 35%  
Age 18–75 | Reported a harmful outcome from the study drug and terminated the study early |
| Estruch (primarily public) (34) | Can a Mediterranean diet prevent cardiovascular disease among those at high risk? | Diet was effective | N = 7,447  
Women — 57%  
Age 55–80 (men) and 60–80 (women)  
Documented BMI, race, smoking | Despite randomisation there were baseline differences in groups |
| Fayad (industry) (35) | Comparison of dalcetrapib versus placebo on atherosclerosis | No significant benefit | N = 130  
Women — 18%  
Age 18–75  
Documented race (white = 93%) | Preponderance of men suggesting inclusion bias |
| Fleshner (industry) (36) | Comparison of dutasteride versus placebo in low-risk prostate cancer | unclear | N = 289  
Single sex condition  
Age 48–81  
Documented race, BMI, anxiety regarding cancer | Complex statistical analyses to look for some benefit for the test medication |
| Author, Funding (public, industry, both), (reference number) | Aim/Question | Outcome | Population characteristics number, sex, race/ethnicity, age, measure of SES | Additional notes on method |
|------------------------------------------------------------|--------------|---------|--------------------------------------------------------------------------|--------------------------|
| Forster (public) (37)                                        | Comparison of structured education program to none for informal caregivers of stroke patients | No differences in patient outcomes | $N=928$ patients | Comments in paper re excess of women as caregivers |
|                                                             |              |         | Women = 44% | | |
|                                                             |              |         | $N=928$ caregivers | | |
|                                                             |              |         | Women = 68% | | |
|                                                             |              |         | Documented race, education, employment | | |
| Gebre (public) (38)                                         | Comparison of twice- or once-yearly treatment for trachoma | No significant difference in outcome | $N=33,190$ | Documented that only predictor of greater infection was greater proportion of girls/women in cluster but did not discuss potential issue of gender equality |
|                                                             |              |         | Women = 48% | | |
|                                                             |              |         | Age > 9 | | |
|                                                             |              |         | Documented distance to hospital | | |
| Griffin (public/industry) (39)                              | Comparison of the impact of less or more intensive treatment of diabetics on CVD after 5 years | No significant difference in outcome | $N=3,057$ | No explanation for how recruitment of diabetics via GP practices yielded no women |
|                                                             |              |         | Women = 0% | | |
|                                                             |              |         | Age 40-69 | | |
|                                                             |              |         | Documented race (white = 96%), unemployment | | |
| Hoffman (public) (40)                                       | Does emergency room use of coronary CT angiography decrease time in hospital for chest pain? | Time in hospital decreased but later testing and radiation increased | $N=1,000$ | Authors call theirs a representative, population-based sample |
|                                                             |              |         | Women = 47% | | |
|                                                             |              |         | Age 40-74 | | |
| Horton (industry) (41)                                      | Cross-over study of thalidomide for cough in severe idiopathic pulmonary fibrosis | Treatment improved cough and respiratory quality of life | $N=23$ | No mention of lack of women in discussing external validity |
|                                                             |              |         | Women = 22% | | |
|                                                             |              |         | Age >50 | | |
|                                                             |              |         | Documented race, BMI | | |
| Kang (public) (42)                                          | Comparison of early surgery versus standard treatment for infective endocarditis | Intervention decreased embolic events and death | $N=76$ | Noted some sex-specific side effects, e.g. cervical dysplasia, menorrhagia |
|                                                             |              |         | Women = 33% | | |
|                                                             |              |         | Age 18-80 | | |
| Karim (public) (43)                                         | Comparison of timing of antiretroviral and TB treatments to prevent AIDS progression | No significant differences arising from timing | $N=429$ | | |
|                                                             |              |         | Women = 51% | | |
|                                                             |              |         | Age >16 | | |
|                                                             |              |         | Documented education, autonomy | | |
| Author, Funding (public, industry, both), (reference number) | Aim/Question | Outcome | Population characteristics number, sex, race/ethnicity, age, measure of SES | Additional notes on method |
|---------------------------------------------------------------|--------------|---------|-----------------------------------------------------------------------------|----------------------------|
| Katz (public) (44)                                            | A comparison of partial meniscectomy versus physiotherapy for symptomatic meniscal tears | No real difference in outcome by intention to treat but 30% of physio group underwent surgery | N = 330<br>Women = 57%<br>Age > 44<br>Documented race, BMI, mood | Not blinded<br>83% of those assessed were not included, reasons not clear |
| Kolle (public/industry) (45)                                  | Comparison of expanded adipose tissue derived stem cells and ordinary fat grafts | Better graft survival with stem cells at 121 days | N = 10<br>Women = 90%<br>Age 18–45 | |
| Lebwohl (industry) (46)                                       | Comparison of a new gel (Ingenol mebutate) with other treatments of actinic keratosis | New treatment was no better than existing ones | N = 1,005<br>Women = 25%<br>Age > 18 | Could have commented that actinic keratosis more common and reported elsewhere to be more treatable in men |
| Lewycka (public and NGOs) (47)                                | Does peer health education of mothers improve breastfeeding rates and lower mortality in rural Malawi? | Unclear – overall – no significant impact | Cluster randomisation: 48 clusters, 26,262 births (?)<br>Age of women: 10–49<br>Recorded tribe, education, occupation, religion, marital status, SES, parity | Designed as a single sex study but men included in groups<br>20% lost to f/u Selected data used to find some benefit to intervention |
| Liem (public) (48)                                            | Can pessary insertion at 16–20 weeks' gestation decrease preterm birth in multiple pregnancy | Pessary did not decrease risks and did increase vaginal discharge | N = 813<br>Single sex condition<br>Documented race, BMI, education | Not blinded |
| Lo-Coco (primarily public, drugs donated by industry) (49)    | Comparison of two drug regimens to treat promyelocytic leukaemia | New drug treatment was no better than old treatment | N = 156<br>Women = 51% | Reported as non-inferior |
| Mallick (public/industry) (50)                                | Comparison of low- and high-dose radioiodine for treating thyroid cancer | No difference in effect and lower dose had fewer side effects | N = 438<br>Women = 74%<br>Age 16–80 | |
| Marchioli (industry) (51)                                     | Comparison of phlebotomy, hydroxurea or both for treatment of lower or higher hematocrits in polycythemia | Those with lower hematocrit had significantly better outcomes, i.e. fewer deaths from cardiovascular or thrombotic events | N = 365<br>Women = 38% | No comment on whether smaller hematocrit elevations have greater impact on health of women |
| Mateos (industry) (52)                                        | Comparison of drug to no drug for smouldering multiple myeloma | Drug more effective than no treatment | N = 119<br>(10% withdrawn from study by researchers)<br>Women = 55% | Phase 3 drug trial<br>Only 42% completed study |
| Author, Funding (public, industry, both), (reference number) | Aim/Question | Outcome | Population characteristics number, sex, race/ethnicity, age, measure of SES | Additional notes on method |
|-----------------------------------------------------------|--------------|---------|--------------------------------------------------------------------------|--------------------------|
| Milstone (public/industry) (53) | A comparison of chlorhexidine and regular baths to decrease bacteraemia in critically ill children | No statistically significant difference found | \(N = 4,947\) sex not specified age <2 months Documented race | Not blinded 371 in treatment group excluded for lack of consent versus none excluded in control group Enrolment biases identified |
| Montalescot (industry) (54) | Does prasugrel prior to rather than at the time of angioplasty post-non-STEMI decrease mortality? | Outcome: no benefit of pre-treatment and greater harm from life-threatening bleeding | \(N = 4,033\) Women = 28% Documented race: (Caucasian = 97%), BMI, health behaviours | Phase 3 drug trial Supplemental data says women more likely than men to bleed \(p = 0.09\) – not reported in paper, itself No explanation for low enrolment of women |
| Motzer (industry) (55) | A comparison of two chemotherapies for metastatic renal cancer | Trial drug was no better than control | \(N = 1,110\) Women = 27% Geographic and ethnic subgroups used for analyses | Trial drug reported as ‘non-inferior’ No documented exclusion criteria yet 300 excluded Protocol changed mid-study Often reported numbers without statistical significance |
| Nguyen-Khac (public) (56) | Comparison of Prednisolone with and without N-acetylcysteine for severe alcoholic hepatitis | No benefit to 2 drug regime | \(N = 174\) Women = 40% Age > 18 | Not blinded |
| O’Dell (public) (57) | A cross-over comparison of 2 second-line treatments for RA | New treatment was no better than old | \(N = 353\) Women = 46% Age > 17 Documented race, BMI, smoking | Study treatment reported as non-inferior Although women responded better to new treatment than expected and similar to men’s response, didn’t comment on this -reported relative risk reduction (30%) rather than absolute |
| Parker (industry) (58) | Assessed efficacy and safety in treating metastatic prostate cancer with radiation vs. placebo | Life expectancy with radiation versus placebo: 14.9 versus 11.3 months. | \(N = 921\), single sex condition Documented race, Many medical exclusions | Not blinded |
| Pickard (public) (59) | Comparison of antimicrobial and regular urethral catheters for short-term use | No significant difference in infection rate | \(N = 6,394\) Women = 62% Age > 15 | No consideration of whether anatomical differences might lead to differences in infection risk for men and women that could have been seen by disaggregating data |
| Author, Funding | Aim/Question | Outcome | Population characteristics, sex, race/ethnicity, age, measure of SES | Additional notes on method |
|----------------|-------------|---------|---------------------------------------------------------------------|--------------------------|
| Pirmohamed (public) (60) | Comparison of genotype guided and standard dosing of warfarin for atrial fibrillation or DVT | Genotype-guided dosing reduced number of days with high INR and time to steady state dosage | N = 455 | Women = 39% |
| Roberts (industry) (61) | Does point of care genetic testing identify those for whom clopidogrel presents a high risk? | Effective identification of carriers of gene | N = 187 | Women = 22% |
| Roe (industry) (62) | Comparison of prasugrel versus clopidogrel for acute coronary syndromes without re-vascularisation | No significant differences found | N = 9,326 | Women = 39% |
| Shaukat (public) (63) | Comparison of long-term outcomes among those undergoing faecal occult blood screening for colon cancer | After 30 years those screened had significantly lower mortality from colon cancer but not lower overall mortality | N = 46,551 | Women = 52% |
| Sihvonen (public) (64) | Comparison of partial meniscectomy and sham operation for degenerative meniscal tear with no osteoarthritis. | No differences in outcomes found | N = 146 | Women = 39% |
| Silbergleit (public) (65) | Comparison of IM midazolam versus IV lorazepam after 5 minutes of seizures | Midazolam of significant benefit | N = 893 | Women = 43% |
| Soofi (NGO/industry) (66) | Can 1 year of zinc - or micronutrients improve growth and limit infection and diarrhoea in infants | Supplemeting with zinc decreased Fe deficiency anaemia but increased side effects | N = 2,746 | Sex unspecified |
| Thiele (public/industry) (67) | Comparison of intra-coronary versus IV abciximab post-STEMI | Of multiple endpoints only heart failure might be improved with intra-coronary treatment | N = 2,065 | Women = 25% |
| Tylleskar (public) (68) | Does peer counselling mothers of infants decrease diarrheal disease by increasing breast feeding in Africa? | No significant decrease in diarrhoea despite increase in breast feeding | N = 2,579 | Sex-specific study |

Additional notes on method:
- Treating physician could exclude subjects for undefined reasons.
- Large enrolment would have allowed for assessing sex differences in side effects like bleeding, but not done.
- Assessed sex-specific relative risks of dying from colon cancer.
- Could have considered whether giving supplements might change food offered to infants and particularly to girls.
- Not blinded.
- Although women had significantly better outcomes than men this was attributed to chance.
- Enrollment bias noted.
- Data on main outcome downplayed and instead authors conclude breast feeding must be beneficial and might shorten course of diarrhoea despite no evidence for this.
| Author, Funding | Aim/Question | Outcome | Population characteristics number, sex, race/ethnicity, age, measure of SES | Additional notes on method |
|----------------|-------------|---------|---------------------------------------------------------------------------|---------------------------|
| Von Hoff (industry) (69) | Comparison of new and standard drug combinations for treating pancreatic cancer | New combination prolonged survival by about 2 months | $N = 861$<br>Women = 42%<br>Age 18+<br>Documented race and region | Phase 3 drug trial |
| Wang 98b (public) (70) | Comparison of ASA + or – clopidogrel for stroke prevention after TIA | Additional drug decreased stroke without increasing haemorrhage | $N = 5,170$<br>Women = 34%<br>Age 40+ years<br>BMI, smoking | Interactions assessed in subgroups and documented |
| Walmsley (industry) (71) | Comparison of new and older combinations of treatments for HIV | New combination reported as more efficient and safer | $N = 833$<br>Women = 16%<br>Age > 18<br>Documented race | Preponderance of men was commented on by authors as arising from exclusion of pregnant or potentially pregnant women |
| White (public/industry) (72) | Comparison of alogliptin versus placebo in diabetics hospitalised for unstable angina or MI | Drug was found to be no better than placebo | $N = 5,830$<br>Women = 32%<br>Documented race, BMI, smoking, region | Reported outcome as non-inferior<br>Stratified results by region<br>Reported sex stratification in appendix |
| Wiviott (industry) (73) | Comparison of prasugrel and clopidogrel post-non-STEMI and without re-vascularisation | Unclear – reported that test drug was beneficial | $N = 7,243$<br>Women = 36%<br>Age < 75 | Phase 3 drug trial<br>No explanation for disproportion of men<br>Women were less likely to be investigated with angiography |
| Young (public) (74) | Can social media networks increase HIV testing among African American and Latino men who have sex with men? | Intervention increased HIV testing | N122<br>Single sex study<br>Age 18+<br>Documented race, education, birthplace, income social connectedness, urban/rural, sex behaviours | |
| Zeuzem (industry) (75) | Comparison of faldaprevir plus deleobuvir at different doses, with or without ribaviron to induce a sustained virologic response in chronic Hep C | Including Ribavirin improved outcome | $N = 362$<br>Women = 48%<br>Documented age, race, BMI | Phase 2 drug study<br>Not blinded<br>Initial trial halted by FDA<br>Changed protocol during study and redefined endpoint<br>Phase 3 trial |
| Zhu (public/industry) (76) | Comparison of vaccine versus placebo to prevent enterovirus infection | The vaccine was effective and produced no more side effects than placebo | $N = 10,245$<br>Girls = 44%<br>Age 6–34 months<br>Documented BMI | |
| Age | Sex/gender | BMI | Health behaviours | Race, ethnicity | SES, education | Other individual characteristics |
|-----|------------|-----|------------------|----------------|---------------|---------------------------------|
| In demographics | | | | | | |
| 23, 26, 27, 29, 33, 37, 40, 41, 42, 45, 46, 50, 51, 59, 60-64, 69, 71, 72, 74 | 20-26, 28, 29-31, 33-35, 36 (sex-specific condition), 37-46, 48, 49-52, 54-57, 58 (sex-specific disease), 59-65, 67, 68 (sex specific), 69-76 | 20, 21, 26, 28 (overweight noted), 31 (weight), 34, 36, 40, 44, 48, 54, 57, 61 (weight), 62 (weight), 64, 68, 70, 72, 73, 75, 76 | 21 (smoker), 26 (smoker), 34 (smoker), 47, 54, 57 (smoker) 60 (smoker), 61 (smoker), 62 (smoker), 70, 72 (smoker), 74 | 20, 22, 23, 29, 31, 34, 35, 39, 36, 37, 39 (93% white), 40, 41, 44, 46 (all white), 47, 48, 53, 54, 57, 58, 60-62, 65, 67 (all white), 69, 71, 72, 74, 75 | 20, 37, 39, 43, 47, 48, 66, 68, 74 | 22 (sexual orientation), 25 (quality of life, depression), 28 (lives alone), 29 (residence), 31 (location), 36 (anxiety re cancer), 37 (employment), 38 (location), 43 (Karnofsky score), 44 (mental health), 47 (social connectedness, marital status), 55 (site), 68 (marital status, community traits), 69 (region), 72 (world region), 74 (birthplace, social connectedness, urban/rural) |
| Among explicit exclusion criteria | 20, 22, 23, 25, 27 (infant study), 28, 29, 31, 33-36, 38-47, 49, 50, 52, 53, 56, 57, 63, 64, 66, 70, 73, 76 | 26 (pregnancy), 32 (pregnant), 36 (sex-specific condition), 39 (no women although not an explicit exclusion), 41 (pregnancy potential), 45 (pregnant), 47 (failed to exclude men), 48 (sex-specific condition), 51 (pregnancy or no contraception), 57 (women without contraception), 60 (pregnancy), 61 (pregnancy), 65 (pregnancy), 67 (pregnancy), 68 (breastfeeding study), 70 (pregnancy), 71 (if no proof not pregnant), 72 (planning pregnancy), 74 (women) | 34 (>40), 40, 45 | 20 (non-smokers), 34 (substance abuse), 45 (smoker), 51, 57 (substance abuse), 72 (drugs, alcohol abuse) | 34 (literacy), 65 (prisoners) | 21 (distance to study centre), 30 (none stated but >1/3 withdrawn by industry researchers during trial without explanation), 31 (no exclusions but more than ½ withdrew due to side effects), 32 (no contraception for either men or women), 34 (possible difficulty following a diet), 44 (English illiteracy), 47 (sterilisation), 52 (none named but >10% of treatment group withdrawn by researchers without explanation), 53 (5-10% withdrawn overall but all from treatment group for lack of consent), 55 (none named but 300 excluded), 65 (weight of children, also more than 2/3 excluded for unnamed reasons), 60 (treating MD determined eligibility), 65 (prisoners) |
public funders are more and more insistent on inclusion (10, 19, 87). The European Commission website on Research & Innovations includes a Gendered Innovations section to support researchers by presenting examples of how to analyse sex and gender aspects in parallel (88). Such resources reaffirm that inclusion alone does not identify impact. Evidence of the differential effect of sex/gender on, for example, cardiovascular disease diagnosis, treatment offered, and prognosis (19, 89), or on pharmaco-dynamics in general is robust enough to recommend inclusion of sufficient numbers of participants to enable subgroup analyses for women and men (13).

Our focus was whether and how sex/gender was addressed in clinical trials rather than whether this social characteristic modifies outcomes for specific interventions or diseases. Whether social circumstances are acknowledged as integral to outcomes and elevated to the level of variables for analysis rather than controlled into oblivion is a matter of methodology across RCTs regardless of their specific topic. We therefore did not limit the sample to studies of particular systems and included all RCTs published in the journals and time frame selected. This yielded a mix of individual and cluster randomised trials; public and private funders; and pharmaceutical, technologic, and educational interventions. To the best of our knowledge, no study prior to ours has systematically assessed sex/gender in formulation of the research question, design, analysis, and interpretation in randomly selected studies from high impact medical journals. The composite picture arising is one of loss of information at each step in the path from design, through recruitment, data analysis and interpretation, a loss that can embed error in evidence.

Research question and design
In general, men and women were included, although over-representation, usually of men relative to women, limited external validity for many of the trials reviewed. The preponderance of men in several studies of diseases with no male prevalence, studies that claimed random recruitment of participants, raises questions about interference in the selection process (54, 73) as did subjective and undefined exclusions (24, 30, 39, 44, 52–55, 60, 72, 73). In one study, the removal of almost 80% of recruits can only be assumed to introduce selection bias (44). As mentioned earlier, arbitrary and ill-defined options to exclude participants at intake or during the study were more common in trials with some or all funding from industry (90%) (24, 30, 39, 52–55, 60, 73) than solely from public sources (44). A European study of interventions to decrease cardiovascular mortality among diabetics did not mention why all participants were men. Being a woman was not among exclusion criteria, recruitment occurred in general practices where women are well represented, neither the interventions the disease studied nor the outcome were specific to men, and there

| Table 2 (Continued) |
|---------------------|
| **Age** | **Sex/gender** |
| 67 (medical conditions), 72 (investigators' opinion re: disability), 75 (1/4 of those screened excluded, without explanation) | 67 (medical conditions), 72 (investigators' opinion re: disability), 75 (1/4 of those screened excluded, without explanation) |
| **BMI** | **Race/ethnicity** |
| **SES, education** | **Other individual characteristics** |
| **Health behaviours** | **67 (medical conditions), 72 (investigators' opinion re: disability), 75 (1/4 of those screened excluded, without explanation)** |

Citation: Glob Health Action 2016, 9: 29597 - http://dx.doi.org/10.3402/gha.v9.29597
Table 3. Addressing sex/gender in reviewed RCTS (N = 57)

|                                                                 | Yes (reference number)                                                                 | No (reference number)                                                                 |
|-----------------------------------------------------------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Sex-specific condition\(^a\)                                    | 36, 47,48, 58,68                                                                       | 20–35, 37–46, 49–57, 59–67, 69–3, 75,76                                               |
|                                                                 | 74 (although HIV not sex-specific target population was gay men)                        |                                                                                       |
| Information on sex/gender of participants documented             | 20–26, 28–30, 33–35, 37–46, 49–52, 54–57, 59–65, 67, 69–73,                            | 27, 31 (proportions of overall cohort reported but not of those who                     |
|                                                                 | 75, 76                                                                                 | completed trial), 32 (incomplete numbers and only in appendix),                      |
|                                                                 |                                                                                       | 53 (children), 66 (children)                                                          |
| Women and men in non-sex-specific studies (n = 51)               |                                                                                       |                                                                                        |
| Overall                                                         | 20–6, 28–30, 33–35, 37–46, 49–52, 54–57, 59–65, 67, 69–73,                            | 27, 31 (noted proportions of whole group but not of group that was                    |
| Proportions of men and women stated                             | 70–73                                                                                 | analysed and completed study), 53, 66                                               |
| Disproportion of men to women, i.e. > or =60:40                  | 20, 24, 32, 33, 35, 39, 42, 46, 51, 54–56, 60–62, 64, 67,                            | 22, 23, 25, 26, 28–30, 34, 37, 38, 40, 43–45, 49, 50, 52, 57, 59, 63,              |
|                                                                 | 73, 75, 76                                                                             | 65, 68, 69, 75, 76                                                                  |
| Disproportion of women to men, i.e. > or =60:40                 | 23, 37 (assuming caregivers were primary participants, rather than patients),        | 20–22, 24–26, 28–30, 32–35, 38–44, 46, 49, 51, 52, 54–57, 60–65,                  |
|                                                                 | 45, 50, 59                                                                             | 67, 69–73, 75, 76                                                                   |
| Proportion of men to women approximately equal, i.e. each at     | 21, 22, 25, 26, 28–30, 34, 38, 40, 43, 44, 49, 52, 57, 63, 65, 69,                 | 20, 23, 24, 32, 33, 35, 37, 39, 41, 42, 45, 46, 50, 51, 54–56, 59–62,              |
| least 40% of sample                                            | 75, 76                                                                                 | 64, 67, 70–73                                                                       |
| Sex/gender included in analysis and/or discussion (n = 57)\(^b\) |                                                                                       |                                                                                        |
| Overall                                                         | 20, 26, 34, 38, 62, 63, 69–72, 75                                                     | 21–25, 27–33, 35–37, 39–61, 64–68, 73, 74, 76                                       |
| Via data disaggregation (separate analyses for women and men)   | 20, 34, 63, 67 (mentioned subgroup analyses), 69–71, 72                              | 21–33, 35–62, 64–66, 73–76                                                          |
|                                                                 | (compared hazard ratios in appendix)                                                   |                                                                                        |
| As an independent variable                                      | 26, 38 (proportion of girls in each cluster) 62 (in appendix), 69,                    | 20–25, 27–37, 39–61, 63–68, 70, 72–74, 76                                           |
|                                                                 | 71, 75                                                                                 |                                                                                        |
| Via interaction with other variables                            | 26, 63, 70                                                                             | 20–25, 27–33, 34 (could have examined gender via known interaction of sex*BMI),      |
|                                                                 |                                                                                        | 35–62, 64–69, 69–71                                                                |
| Sex/gender included in interpretation/discussion               | 20, 48 (commented re benefit of a low cost intervention), 51, 54 (comment in        | 21–25, 26 (despite excellent methodology), 27–46, 47 (confusing analysis but didn’t   |
|                                                                 | supplement that women had more adverse outcomes), 57 (one statement), 60 (disproportion | appear to discuss social traits), 49, 50, 52, 53, 55, 56, 58, 59, 61, 62, 64, 65,  |
|                                                                 | of men mentioned), 63, 67 (dismissed significant gender differences as likely due to   | 66 (no consideration of whether girl                                                   |
|                                                                 | 71 (disproportion of men mentioned, as was same outcomes both sexes)                  | children might be systemically disadvantaged, i.e. whether giving                     |
|                                                                 |                                                                                        | supplements might precipitate parental redirecting of food to other children), 68     |
|                                                                 |                                                                                        | (one statement that SES was not a confounder), 69, 70, 72–76                        |

\(^a\)Conditions affecting either men or women but not both.

\(^b\)Includes studies of sex-specific conditions.
was no indication in the title or abstract of the exclusion of women (39). This was the sole study to demonstrate a total blindness to sex/gender that was criticised widely and became a reason for denial of public funding more than 20 years ago in the United States (90). In contrast, a study of whether social networking can increase HIV testing among African- and Latino-Americans intentionally limited research on a non-sex-specific illness or intervention to men who have sex with men (74). By being explicit about reasons for selecting an all-male population, the authors minimised bias in their research question. The study by Lewycka et al. (47) on whether peer health education of women could increase breastfeeding rates and decrease morbidity or mortality in Malawi illustrates sex/gender bias via over-inclusion. Allowing men to attend peer groups for women in a setting where women generally lack autonomy created the potential for silencing or coercion of female by male participants. Put another way, having men participate in what should be a study of women’s health education introduced potential bias arising from gender inequality. This was not considered in the paper.

Analysis and interpretation

Data related to sex/gender, although available, were often neither utilised nor discussed. Authors might argue that such data served as evidence that randomisation controlled the impact of baseline characteristics like sex/gender via equal distribution and that funding limitations precluded powering studies to examine different outcomes for women and men. However, one could suggest that such an argument is evidence of, and will perpetuate blindness to the impact of sex/gender on health outcomes. There were no examples of a priori consideration of sex/gender by randomisation within the groupings ‘men’ and ‘women’ rather than in the sample as a whole. In the 8 studies where results were disaggregated for men and women these findings were generally not discussed and none considered reasons for sex/gender differences (20, 34, 63, 67, 69–72). This silence, although methodologically appropriate (because subgroup analysis was not planned a priori) occurred in studies where enrolment was adequate to identify differences and so, a research opportunity was lost. Three examples illustrate this. A study of new drug regimens for rheumatoid arthritis found women’s responses equalled those for men (57). The authors noted that in prior research men had responded better than women to treatment, but made no comment about their novel findings and instead stated that there was no sex differential in response. In a study of interventions immediately following a STEMI (a kind of myocardial infarction) statistically significant differences in response by women and men were dismissed as a chance finding (67). Finally, although the only predictor of prevalence of trachoma infection was the proportion of women in each randomised cluster studied ($p = 0.002$), this was ignored while statistically insignificant variability across treatments ($p > 0.99$) was summarised as possibly of importance (38).

At times, authors’ statements did not match findings, putting a positive spin on interventions of no benefit or possible harm. New treatments that were no better than controls were termed ‘non-inferior’ (see comments in Table 1). Although overstating benefit was most common in tests of new drugs, two publicly funded studies highlight how unshakeable beliefs shaped reporting (47, 68). Both studies assumed that increasing breastfeeding rates would improve infant health in Africa. In each, the proportion of breastfed babies did increase; however, when there was no subsequent change in designated health outcomes authors hypothesised that there were likely other, non-measured advantages to breastfeeding. The evidence of no benefit from breastfeeding was, for whatever reasons, deemed unacceptable to report.

Social characteristics such as sex/gender are not always modifiers of the relationship between interventions and health outcomes. In treatment trials for endocarditis (42) or pancreatic cancer (69), sex/gender as a determinant or an effect modifier seemed unlikely. However, when sex/gender, race or SES matter will not be detected by randomising them into hiding. Without comment from authors it is impossible to determine what reasoning preceded limiting analyses to the group as a whole or if the impact of social circumstances was considered. Only by including subgroup analyses can researchers ascertain whether and when the measurement of social traits is relevant.

Limitations

Drawing general conclusions about research methodology from analyses of 57 studies must be done with caution. However, by randomly selecting among the 712 RCTs identified, the sample studied should be representative of all papers identified in the initial search. In addition, interim findings after analysing 28 of 57 papers did not change substantially when all reports were included, making it seem that we had identified a pattern and could generalise from it.

One might argue it is difficult to analyse research from the varying medical areas included in this review in the same way. However, the point here was not to evaluate the relevance or best way to analyse sex/gender in one and each disease or condition. Instead, we searched for patterns and an overview of whether researchers seem aware of, and addressed, the fact that the groups men and women are not identical but instead often differ with respect to important biological characteristics and social and environmental living conditions.

Conclusion

Few of the random samples of all RCTs published in five high-impact journals over 5 years assessed whether social
circumstances altered outcomes. Fewer still attempted to interrogate findings with respect to sex/gender (or race or SES) and identify whether sex/gender acts as a modifier of the pathway from intervention to outcome. The theoretical robustness of the RCT is that it mimics animal experiments by controlling for, or randomly distributing and, therefore, removing unidentified and unmeasured human variability as sources of error. Baseline characteristics such as SES, race and sex/gender are, however, known determinants of health that can modify the relationship between exposures and outcomes of primary interest. Inherent in the methodology of clinical trials is the clean slate of equal background noise or impact of social characteristics like gender in all study arms but also the messiness of failing to hear the noise. It is only by listening by studying rather than randomising non-biological traits away, that research will identify whether and when social characteristics of participants affect outcomes.

Acknowledgements

Both authors wish to thank the Umeå Centre for Gender Studies for supporting this research.

Authors’ contributions

Both authors designed the research and reviewed and analysed data. SPP carried out the literature search/data extraction and drafted the paper which was then reviewed and revised by KH.

Conflict of interest and funding

The authors have not received any funding or benefits from industry or elsewhere to conduct this study.

References

1. Koskinen S, Martelin T. Why are socioeconomic mortality differences smaller among women than among men? Soc Sci Med 1994; 38: 1385–96.
2. Krieger N, Smith GD. Bodies count and body counts: social epidemiology and embodying inequality. Epidemiol Rev 2004; 26: 92–103.
3. Phillips SP. Measuring the health effects of gender. J Epidemiol Community Health 2008; 62: 368–71.
4. Connell RW. Gender. Cambridge: Polity Press; 2002.
5. Ridgeway CL, Correll SJ. Unpacking the gender system: a theoretical perspective on gender beliefs and social relations. Gen Soc 2004; 18: 510–31.
6. Thorlund M, Wastesson JW, Agahi N, Lagergren M, Parker MG. The rise and fall of women’s advantage: a comparison of national trends in life expectancy at 65 years. Eur J Ageing 2013; 10: 271–7.
7. Courtenay WH. Constructions of masculinity and their influence on men’s well-being: a theory of gender and health. Soc Sci Med 2000; 50: 1385–401.
8. Seifarth JE, McGowan CL, Milne KJ. Sex and life expectancy. Gend Med 2012; 9: 390–401.
9. Lorber J, Moore LJ. Gender and the social construction of illness. New York: AltaMira Press; 2002.
10. Kaufman JS, MacLehose RF. Which of these is not like the others? Cancer 2013; 119: 4216–22.
11. Maas AHEM, van der Schouw YT, Regitz-Zagrosek V, Swahn E, Appelman YE, Pasterkamp G, et al. Red alert for women’s heart: the urgent need for more research and knowledge on cardiovascular disease in women. Proceedings of the Workshop held in Brussels on Gender Differences in Cardiovascular disease, 29 September 2010. Eur Heart J 2011; 32: 1362–8.
12. Arnetz L, Ekberg NR, Alvarsson M. Sex differences in type 2 diabetes: focus on disease course and outcomes. Diabetes Metab Syndr Obes 2014; 16: 409–20.
13. Regitz-Zagrosek V, editor. Sex and gender differences in pharmacology. Berlin: Springer-Verlag; 2012.
14. Nyberg F, Osika I, Evengård B. “The Laundry Bag Project” – unequal distribution of dermatological healthcare resources for male and female psoriatic patients in Sweden. Int J Dermatol 2008; 47: 144–9.
15. Hamberg K. Gender bias in medicine. Women’s Health 2008; 4: 237–43.
16. Borkhoff CM, Hawker GA, Kreder HI, Glazier RH, Mahomed NN, Wright JG. The effect of patients’ sex on physicians’ recommendations for total knee arthroplasty. CMAJ 2008; 178: 681–7.
17. Kreatsoulas C, Anand S. Considering race/ethnicity and socioeconomic status in randomized controlled trials. A commentary on Frampton et al.’s systematic review generalizing findings and tackling health disparities in asthma research. Soc Sci Med 2009; 69: 1155–6.
18. Phillips SP, Hamberg K. Women’s relative immunity to the socioeconomic health gradient: artifact or real? Glob Health Action 2015; 8: 27259, doi: http://dx.doi.org/10.3402/gha.v8.27259
19. Swahn E. Stable or not, woman or man: is there a difference? Eur Heart J 2012; 33: 2769–70.
20. Aberle DR, DeMello S, Berg CD, Black WC, Brewer B, Church TR, et al. Results of the two incidence screenings in the National Lung Screening Trial. N Engl J Med 2013; 369: 920–31.
21. Anderson DR, Dunbar MJ, Bohm ER, Belzile E, Kahn SR, Zukor D, et al. Aspirin versus low-molecular-weight heparin for extended venous thromboembolism prophylaxis after total hip arthroplasty: a randomized trial. Ann Intern Med 2013; 158: 800–6.
22. Boyd MA, Kumarasamy N, Moore CL, Nwizu C, Losso MH, Mohapi L, et al. Ritonavir-boosted lopinavir plus nucleoside or nucleotide reverse transcriptase inhibitors versus ritonavir-boosted lopinavir plus raltegravir for treatment of HIV-1 infection in adults with virological failure of a standard first-line ART regimen (SECOND-LINE): a randomised, open-label, non-inferiority study. Lancet 2013; 381: 2091–9.
23. Burmester GR, Blanco R, Charles-Schoeman C, Wollenhaupt J, Zerbini C, Benda B, et al. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. Lancet 2013; 381: 451–60.
24. Byrd JC, Furman RR, Coutre SE, Flinn IW, Burger JA, Blum KA, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med 2013; 369: 32–42.
25. Chakravarthy U, Harding SP, Rogers CA, Downes SM, Lotery AJ, Culliford LA, et al. Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial. Lancet 2013; 382: 1258–67.
26. Cooper CJ, Murphy TP, Cutlip DE, Jamerson K, Henrich W, Reid DM, et al. Stenting and medical therapy for atherosclerotic renal-artery stenosis. N Engl J Med 2014; 370: 13–22.

27. Cotton MF, Violiari A, Otowmbe K, Panchia R, Dobbels E, Rabie H, et al. Early time-limited antiretroviral therapy versus deferred therapy in South African infants infected with HIV: results from the children with HIV early antiretroviral (CHER) randomised trial. Lancet 2013; 382: 1555–63.

28. Dennis M, Sandercock P, Reid J, Graham C, Forbes J, Murray G. Effectiveness of intermittent pneumatic compression in reduction of risk of deep vein thrombosis in patients who have had a stroke (CLOTS 3): a multicentre randomised controlled trial. Lancet 2013; 382: 516–24.

29. Devanand DP, Mintzer J, Schultz SK, Andrews HF, Sultzter DL, de la Pena D, et al. Relapse risk after discontinuation of risperidone in Alzheimer's disease. N Engl J Med 2012; 367: 1497–507.

30. Doody RS, Raman R, Farlow M, Iwatsubo T, Vellas B, Joffe S, et al. A phase 3 trial of semagacestat for treatment of Alzheimer's disease. N Engl J Med 2013; 369: 341–50.

31. Dooley MA, Jayne D, Ginzler EM, Isenberg D, Olsen NJ, Wofsy D, et al. Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. N Engl J Med 2011; 365: 1886–95.

32. Douillard JY, Oliner KS, Siena S, Tabernero J, Burkes R, Barigel M, et al. Pantitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. N Engl J Med 2013; 369: 1023–34.

33. Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ, et al. Dabigatran versus warfarin in patients with mechanical heart valves. N Engl J Med 2013; 369: 1206–14.

34. Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med 2013; 369: 1279–90.

35. Fayad ZA, Mani V, Woodward M, Kallend D, Abt M, Burgess T, et al. Safety and efficacy of dalteparin on atherosclerotic disease using novel non-invasive multimodality imaging (dal-PLAQUE): a randomised clinical trial. Lancet 2011; 378: 1547–59.

36. Fleschner NE, Lucia MS, Egerdie B, Aaron L, Eure G, Nandy I, et al. Dutasteride in localised prostate cancer management: the REDEEM randomised, double-blind, placebo-controlled trial. Lancet 2012; 379: 1103–11.

37. Forster A, Dickerson J, Young J, Patel A, Kalra L, Nixon J, et al. A structured training programme for caregivers of inpatients after stroke (TRACS): a cluster randomised controlled trial and cost-effectiveness analysis. Lancet 2013; 382: 2069–76.

38. Gebre T, Ayele B, Zerihun M, Genet A, Stoller NE, Zhou Z, et al. Comparison of annual versus twice-yearly mass azithromycin treatment for hyperendemic trachoma in Ethiopia: a cluster-randomised trial. Lancet 2012; 379: 143–51.

39. Griffin SJ, Borch-Johnsen K, Davies MJ, Khunti K, Rutten GE, Sandøe A, et al. Effect of early intensive multifactorial therapy on 5-year cardiovascular outcomes in individuals with type 2 diabetes detected by screening (ADDITION-Europe): a cluster-randomised trial. Lancet 2011; 378: 156–67.

40. Hoffmann U, Truong QA, Schoenfeld DA, Chou ET, Woodward PK, Nagurney JT, et al. Coronary CT angiography versus standard evaluation in acute chest pain. N Engl J Med 2012; 367: 299–308.

41. Horton MR, Santopietro V, Mathew L, Horton KM, Politio AJ, Liu MC, et al. Thalidomide for the treatment of cough in idiopathic pulmonary fibrosis: a randomized trial. Ann Intern Med 2012; 157: 398–406.

42. Kang DH, Kim YJ, Kim SH, Sun BJ, Kim DH, Yun SC, et al. Early surgery versus conventional treatment for infective endocarditis. N Engl J Med 2012; 366: 466–73.

43. Karim SSA, Naidoo K, Grobler A, Padayatchi N, Baxter C, Gray AL, et al. Integration of antiretroviral therapy with tuberculosis treatment. N Engl J Med 2011; 365: 1492–501.

44. Katz JN, Brophy RH, Chaissone CE, de Chaves L, Cole BJ, Dahm DL, et al. Surgery versus physical therapy for a meniscal tear and osteoarthritis. N Engl J Med 2013; 368: 1675–84.

45. Kelle SF, Fischer-Nielsen A, Mathiasen AB, Elberg J, Olliiveri RS, Glovinski PV, et al. Enrichment of autologous fat grafts with ex-vivo expanded adipose tissue-derived stem cells for graft survival: a randomised placebo-controlled trial. Lancet 2013; 382: 1113–20.

46. Lebwohl M, Swanson N, Anderson LL, Melgaard A, Xu Z, Berman B. Ingenol mebutate gel for actinic keratosis. N Engl J Med 2012; 366: 1010–19.

47. Lewycka S, Mwasambo C, Rosato M, Kazembe P, Phiri T, Mangana A, et al. Effect of women's groups and volunteer peer counselling on rates of mortality, morbidity, and health behaviours in mothers and children in rural Malawi (MaiMwana): a factorial, cluster-randomised controlled trial. Lancet 2013; 381: 1721–35.

48. Liem S, Schuit E, Hegeman M, Bais J, de Boer K, Bloemenkamp K, et al. Cervical pessaries for prevention of preterm birth in women with a multiple pregnancy (ProTWIN): a multicentre, open-label randomised controlled trial. Lancet 2013; 382: 1341–9.

49. Lo-Cocco F, Avissati G, Vignetti M, Thiede C, Orlando SM, Iacobelli S, et al. Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. N Engl J Med 2013; 369: 111–21.

50. Mallick U, Harner C, Yap B, Wadley J, Clarke S, Moss L, et al. Ablation with low-dose radioiodine and thyrotropin alpha in thyroid cancer. N Engl J Med 2012; 366: 1674–85.

51. Marchioli R, Finazzi G, Specchia G, Cacciola R, Cavazzina R, Cilloni D, et al. Cardiovascular events and intensity of treatment in polycythemia vera. N Engl J Med 2013; 368: 22–33.

52. Mateos MV, Hernández MT, Giraldo P, de la Rubia J, de Arriba F, López Corral L, et al. Lenalidomide plus dexamethasone for high-risk smoldering multiple myeloma. N Engl J Med 2013; 369: 438–47.

53. Milstone AM, Elward A, Song X, Zerr DM, Orscheln R, Speck K, et al. Daily chlorhexidine bathing to reduce bacteraemia in critically ill children: a multicentre, cluster-randomised, cross-over trial. Lancet 2013; 380: 1099–106.

54. Montalescot G, Bolognese L, Dudek D, Goldstein P, Hamm C, Tanguay JF, et al. Pretreatment with prasugrel in non-ST-segment elevation acute coronary syndromes. N Engl J Med 2013; 369: 999–1010.

55. Motrzer RJ, Hutson TE, Cella D, Reeves J, Hawkins R, Guo J, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med 2013; 369: 722–31.

56. Nguyen-Khac E, Thevenot T, Piquet MA, Benferhat S, Goria O'Dell JR, Mikuls TR, Taylor TH, Ahluwalia V, Brophy M, O'Sullivan JM, Fossa˚t, et al. Mycophenolate versus azathioprine as main-
60. Pirmohamed M, Burnside G, Eriksson N, Jorgensen AL, Toh CH, Nicholson T, et al. A randomized trial of genotype-guided dosing of warfarin. N Engl J Med 2013; 369: 2294–303.

61. Roberts JD, Wells GA, Le May MR, Labinaz M, Glover C, Froeschl M, et al. Point-of-care genetic testing for personalisation of antiplatelet treatment (RAPID GENE): a prospective, randomised, proof-of-concept trial. Lancet 2012; 379: 1705–11.

62. Roe MT, Armstrong PW, Fox KA, White HD, Prabhakaran D, Goodman SG, et al. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. N Engl J Med 2012; 367: 1297–309.

63. Shaukat A, Mengin SJ, Geisser MS, Lederle FA, Bond JH, Silbergleit R, Durkalski V, Lowenstein D, Conwit R, Pancioli Susan P, Phillips and Katarina Hamberg Tylleskär T, Jackson D, Meda N, Engebretsen IM, Chopra M, Thiele H, Woehrle J, Hambrecht R, Rittger H, Birkemeyer Soofi S, Cousens S, Iqbal SP, Akhund T, Khan J, Ahmed I, et al. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Wang Y, Wang Y, Zhao X, Liu L, Wang D, Wang C, et al. Walmsley SL, Antela A, Clumeck N, Duiculescu D, Eberhard Wiviott SD, White HD, Ohman EM, Fox KA, Armstrong PW, Zheng SD, Cumberland WG, Lee SJ, Jaganath D, Szekeres G, Costes T. Social networking technologies as an emerging tool for HIV prevention: a cluster randomized trial. Ann Intern Med 2013; 159: 318–24.

64. Zeuzem S, Soriano V, Aseelah T, Bronowicki JP, Lohse AW, Mullhaupt B, et al. Faldaprevir and deleobuvir for HCV genotype 1 infection. N Engl J Med 2013; 369: 630–9.

65. Zhu FC, Meng FY, Li JX, Li XL, Mao QY, Tao H, et al. Efficacy, safety, and immunology of an inactivated alum-adjuvant enterovirus 71 vaccine in children in China: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2013; 381: 2024–32.

66. Hoel AW, Kayssi A, Brahmanandam S, Belkin M, Conte MS, Nguyen LL, et al. Under-representation of women and ethnic minorities in vascular surgery randomized controlled trials. J Vasc Surg 2009; 50: 349–54.

67. Furler J, Magin P, Pirotta M, van Driel M. Participant demographics reported in “table 1” of randomized controlled trials: a case of “inverse evidence”? Int J Equity Health 2012; 11: 14.

68. Vadav AM, Lafleur B, Tong C, Bradshaw R, Marts SA. Women subjects in NIH-funded clinical research literature: lack of progress in both representation and analysis by sex. J Women's Health Gend Based Med 2000; 9: 495–504.

69. Geller SE, Koch A, Pellettiere B, Carnes M. Inclusion, analysis, and reporting of sex and race/ethnicity in clinical trials: have we made progress? J Women's Health 2011; 20: 315–20.

70. Geller SE, Adams MG, Carnes M. Adherence to federal guidelines for reporting of sex and race/ethnicity in clinical trials. J Women's Health 2006; 15: 1123–31.

71. Jagsi R, Motomura AR, Amamath S, Jankovic A, Sheets N, Abel PA. Under-representation of women in high-impact published clinical research. Cancer 2009; 115: 3293–301.

72. Weinberger AH, McKee SA, Mraz C, Inclusion of women and gender-specific analyses in randomized clinical trials of treatments for depression. J Women's Health 2010; 19: 1727–32.

73. Johnson SM, Karvonen CA, Phelps CL, Nader S, Sanborn BM. Assessment of analysis by gender in the Cochrane reviews as related to treatment of cardiovascular disease. J Women's Health 2003; 12: 449–57.

74. Yang Y, Carlin AS, Faustino PJ, Motta MI, Hamad ML, He R, et al. Participation of women in clinical trials for new drugs approved by the Food and Drug Administration in 2000–2002. J Women's Health 2009; 18: 303–10.

75. Ramasubbu K, Gurm H, Litaker D. Gender bias in clinical trials: do double standards still apply? J Women's Health Gend Based Med 2001; 8: 757–64.

76. Epstein S. Inclusion. The politics of difference in medical research. Chicago, IL: The University of Chicago Press; 2007.

77. European Commission. Research & Innovations, SW AFS. Gendered innovations. Sex and gender policies of major granting agencies. Available from: http://ec.europa.eu/research/swafs/gendered-innovations/index_en.cfm?pg=home [cited 19 January 2016].

78. Johnston N, Bornefalk-Hermansson A, Schenk-Gustafsson K, Held C, Goodman SG, Yan AT, et al. Do clinical factors explain persistent sex disparities in the use of acute reperfusion therapy in STEMI in Sweden and Canada? Eur Heart J Acute Cardiovasc Care 2013; 2: 350–8.

79. National Institutes of Health. NIH guidelines on the inclusion of women and minorities as subjects in clinical research. Fed Regist. 1994; 59: 14508–13.