A framework to analyse gender bias in epidemiological research

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The design and analysis of research may cause systematic gender dependent errors to be produced in results because of gender insensitivity or androcentrism. Gender bias in research could be defined as a systematically erroneous gender dependent approach related to social construct, which incorrectly regards women and men as similar/different. Most gender bias can be found in the context of discovery (development of hypotheses), but it has also been found in the context of justification (methodological process), which must be improved. In fact, one of the main effects of gender bias in research is partial or incorrect knowledge in the results, which are systematically different from the real values. This paper discusses some forms of conceptual and methodological bias that may affect women’s health. It proposes a framework to analyse gender bias in the design and analysis of research carried out on women’s and men’s health problems, and on specific women’s health issues. Using examples, the framework aims to show the different theoretical perspectives in a social or clinical research context where forms of selection, measurement and confounding bias are produced as a result of gender insensitivity. Finally, this paper underlines the importance of re-examining results so that they may be reinterpreted to produce new gender based knowledge.

Breaking with prejudices and reconstructing the object of research requires a different way of seeing, in the light of which common-sense knowledge is reconstructed as a form of bias.

Ann Oakley

Gender bias is defined as the differential medical treatment of men and women, the impact of which may be positive, negative or neutral. For research purposes, it should be considered that research design and analysis may lead to systematic errors in the results because of gender insensitivity or androcentrism (the practice of giving overriding importance to male human beings or to the masculine point of view on the world, its culture and its history). Gender insensitivity or androcentrism are unfounded forms of prejudice. Consequently, gender bias in research could be defined as a systematic erroneous gender dependent approach related to social construct, which erroneously regards women and men as similar/different. In turn, this bias produces mistaken or partial knowledge in the results, which are systematically different from the real values. Gender bias may cause inequitable responses from health services and discrimination against one sex or the other.

Gender bias may occur at any stage during the inferential process. Moreover, gender bias may even be found in published results, often because data are not always sex stratified. As a result, research, health promotion and preventive/health-care services and political agendas rarely mention the processes that account for sex differences and gender inequalities.

Most gender bias is to be found in the context of discovery. The biased production of new knowledge is indirectly evidenced by the lack of research and scientific literature concerning some of the significant issues related to women’s health, such as gender violence, illegal abortion and occupational health. Not indicating the susceptibility of women to certain diseases that are common in both sexes is another gender bias of knowledge, such as the false belief that more men suffer chronic obstructive pulmonary disease than women.

Most of the research on gender bias is based on the feminist empiricism, which argues that sexism and androcentrism are forms of social bias that may be corrected by adhering more strictly to the existing methodological norms of scientific inquiry. The aim of the feminist empiricism is to remove blinders and bias in order to produce better accounts of the world. Meanwhile, the main consequence of gender bias in research is the lack of valid results. Therefore, this paper wishes to underline the need for methodological rules to be correctly applied in order to eliminate gender bias from the development of hypotheses and the interpretation stages of data so that more realistic results may be obtained.

Abbreviations: AIGH, American Conference of Governmental Industrial Hygienists; AOR, adjusted odds ratios; CE, clinical epidemiology; CI, confidence intervals; D, differences; DSM, Diagnostic and statistical manual of mental disorders; E, equality; EDNOS, eating disorders not otherwise specified; IRS, information retrieval system; IPV, intimate partner violence; MB, measurement bias; MeSH, medical subject headings; OR, odds ratios; PTSD, post-traumatic stress disorder; RCTs, randomised controlled trials; RR, relative risk; SB, selection bias; SE, social epidemiology; TLVs, threshold limit values.

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A FRAMEWORK TO ANALYSE GENDER BIAS IN RESEARCH ON WOMEN’S AND MEN’S HEALTH PROBLEMS

Eight different theoretical and practical positions related to research that include men and women are presented within a framework (see fig 1) and are illustrated with examples or cases in order to show the relation between epidemiological bias and gender bias in a social or clinical context.

The relation between biological sex, gender as a social construct and health is complex. Perhaps as a result, the likeness of diseases and their determinants in natural and social history is unquestionably accepted, when, in fact their similarities are few (boxes 1 to 4 in fig 1). Furthermore, the existence of important differences between sexes (boxes 5 to 8 in fig 1), as well as between different groups of women and different groups of men is also accepted. These erroneous assumptions of equality or differences between sexes, in the natural history, clinical course and behaviour of diseases, may produce biased knowledge that will condition discriminatory professional practice towards one sex or the other in healthcare services, as well as in health promotion and preventive services and political agendas.

INCORRECTLY ASSUMING EQUALITY BETWEEN WOMEN AND MEN

One way in which health service delivery and research can involve gender bias is by assuming that women’s and men’s health situations and risks are similar, when in fact they are not.13

Incorrectly assuming equality between women and men (E): measurement bias (MB) in social epidemiology (SE) (box 1)

Example of familialism bias

Extreme gender insensitivity in research involves ignoring sex as an important social variable.2 The aggregate bias, also known as the familialism bias, frequently occurs in research on informal care. Since the family is considered to be the smallest unit of analysis, it is individually given the attribute of caring for the family unit, for instance, when it is said that “the family cares for its children and elderly,” although, it is mainly the woman who carries out such tasks. Furthermore, research does not generally identify which family member carries out these reproductive tasks.

An international review of literature on elderly cancer patients and the consequences of their disease for their partners and families identified 165 references, some of which considered gender as a principal determinant of coping and psychological wellbeing.

The results presented were related to differences by sex (that is, differential effect of the social support received according to the sex of the patient, more emotional stress in women carers or the differences found in the use of external support), however gender analysis was not included as a key issue in the interpretation of the results. Therefore, the differing contributions that women and men made within the family and the different effects that caring for a cancer patient had on both sexes were obscured by the terms family, relatives and family members used in the review.13

Incorrectly assuming equality between women and men (E): selection bias (SB) in social epidemiology (SE) (box 2)

Example of under-representation of women in research on chemical risks

Protecting the health of workers is the aim of occupational chemical risk evaluations. However, a selection bias because of gender insensitivity may influence the threshold limit values (TLVs) of these risk evaluations, since no specific information is available regarding chemical substances and women. The TLVs
Figure 1. The three-dimensional matrix in which epidemiological bias (selection or measurement), epidemiological context (clinical or social) and gender bias (incorrectly assuming equality or differences between women and men) can be expected to influence the outcomes in a positive or negative way.

SB = selection bias  
MB = measurement bias  
SE = social epidemiology  
CE = clinical epidemiology  
E = incorrectly assuming equality between women and men  
D = incorrectly assuming differences between women and men
do not consider sex differences despite the obvious metabolic differences between the sexes that may affect their reactions to exposure. Consequently, the values given are the same for both sexes in most countries as well as for the ACIGH (American Conference of Governmental Industrial Hygienists).

This is the case of the non-sex specific chemical risk evaluation in an occupation that is typical to women, hair-dressing.\textsuperscript{14,15} In addition, the reference values are not applicable as they focus on inhalation risks, and do not consider the risk of cutaneously absorbed chemicals used in this occupation. Moreover, these values have been set for specific chemicals used in an 8-hour working day, but not for chemical compounds that a hairdresser would usually use for working days that last longer than 8 hours and where work is often concentrated at the weekends and in shifts. Also, the different responses from pregnant women workers have not been taken into account in the setting of these limits.\textsuperscript{14,15}

Incorrectly assuming equality between women and men (E): selection bias (SB) in clinical epidemiology (CE) (box 3)

Example of under-representation of women in clinical trials

In relation to clinical epidemiology, sex differences in pharmacokinetics and pharmacodynamics are widely recognised.\textsuperscript{16,17} However, a classic gender selection bias in clinical research is because women are poorly represented in the samples of randomised controlled trials (RCTs).\textsuperscript{18–21} Women’s participation in RCTs is lower in the early phases of the studies in which safety, a safe dosage range and side effects are determined. Fleisch et al reviewed the 2001 issues of three leading clinical pharmacology journals publishing early phase drug trials. In all, 239 studies including 15 880 subjects were evaluated. Thirty-one studies tested drugs with already published differences in pharmacokinetics and adverse reactions, in only 9% (2/22) of which had a gender specific analysis been performed. This outlines the need for women’s inclusion at these early phases.\textsuperscript{19}

Incorrectly assuming equality between women and men (E): measurement bias (MB) in clinical epidemiology (CE) (box 4)

Example of lack of sex stratified information in clinical trials

The lack of sex stratification could produce erroneous measurement and misleading results on the efficacy and effectiveness of drugs used for women’s health. This is shown in systematic review papers.\textsuperscript{22} Furthermore, these are the cases of RCT drug therapy for myocardial infarction and rofecoxib.\textsuperscript{18,20} In order to avoid partial knowledge on the efficacy and effectiveness of drugs in women, the following steps have been proposed:\textsuperscript{19}

- Sex distribution, which reflects the patient population likely to receive the therapy
- Subgroup analysis of men and women to permit meta-analyses
- Interaction analysis that enables differences between sexes to be determined
- Discussions that include gender related contents to establish the limits to which the results can be generalised to the population outside the trial or to underline the differences in responses by sex.

**INCORRECTLY ASSUMING DIFFERENCES BETWEEN WOMEN AND MEN**

The second way in which gender bias may exist in health service delivery and research is by assuming differences where there are actually similarities.\textsuperscript{11}

**Incorrectly assuming differences between women and men (D): selection bias (SB) in social epidemiology (SE) (box 5)**

Example of gender bias related to the selection of women as subject of eating disorders studies

By analysing some recently published systematic reviews, it can be seen that studies on eating disorders involve a selection bias, as women and not men are explicitly included.\textsuperscript{21,22} Additionally, the definition of the new Diagnostic and statistical manual of mental disorders (DSM-IV) diagnostic category known as eating disorders not otherwise specified (EDNOS) is based on the assumption that such disorders can only be found in women,\textsuperscript{23} which may thus affect the EDNOS prevalence.\textsuperscript{24}

**Incorrectly assuming differences between women and men (D): measurement bias (MB) in social epidemiology (SE) (box 6)**

Examples of gender bias related to changes in DSM diagnostic criteria

Different reasons such as biological vulnerability, different coping styles, family history and personality traits\textsuperscript{25} among others, have been argued to explain why post-traumatic stress disorder (PTSD) may be more common in women than in men (13% in females and 6.2% in males)\textsuperscript{26} when they are exposed to adverse traumatic events. One fundamental question addressed in the analyses of this sex related difference is whether differential rates of PTSD could be the result of differential exposure to events and not necessarily to differences in the development of PTSD, since the diagnosis of PTSD is dependent upon the presence of an adverse (traumatic) event.

Consideration should be given to certain new types of traumatic events not included in earlier questionnaires or scales but contained in the DSM-IV, which encompass other events beyond natural disasters, wars, torture or kidnapping. Such is the case for rape, which is obviously far more common in women than in men, as well as other forms of sexual abuse and interpersonal violence, which are also more commonly associated with PTSD when compared to accidents or natural disasters.\textsuperscript{27} In fact, women are at a greater risk of PTSD than men following exposure to rape (32% compared to 6% in men).\textsuperscript{28} The overall risk of PTSD depends on the stressor definition and the methods used to measure exposure to specific types of traumatic events. There is consistent evidence of sex differences in the distribution of exposure across specific types of events, while different types of trauma carry different risks for the development of PTSD. As such, much of the increased prevalence of PTSD in women may be affected by trauma type. However, the assumption that women are exposed to fewer traumatic events than men is difficult to understand as an important variation across “types of traumatic events” due to information bias in the questionnaires does not inquire about relevant risks for women.

**Incorrectly assuming differences between women and men (D): selection bias (SB) in clinical epidemiology (CE) (box 7)**

Example of gender bias in ferritin reference values

The assumption that it is normal to find lower values for certain clinical parameters in women than in men may constitutes a gender bias that should be addressed by medicine in order to adapt the normal value or reference limits to clinical parameters of health related quality of life.\textsuperscript{31,32} That menstruating women have up to one million red blood cells fewer than a man has been accepted as “natural” because of their monthly blood loss. It may be true that women are different from men in general but there may still be many women with undetected deficiencies.
Based on research results, the ranges of “normal values” have changed in the past few years, which is reflected in the main internal medicine books. However, many laboratories use the euphemism “reference values,” which depend on the population attended by the centre, instead of referring to “normal values.” This denomination is confusing for health professionals who are required to interpret these reference values as they may be mistaken for normal values.33 34 Once again, gender bias may also be the result of dispersed results of certain clinical parameters. An example of this is the wide dispersion of normal values for parameters related to bone marrow iron stores.35 Although the normal accepted value for the indicator of the iron storage protein ferritin is 50–200 ng/ml, it is surprising to observe the dispersion of the reference values used by different clinical analysis laboratories (table 1), with higher values in men than in women.

Incorrectly assuming differences between women and men (D): measurement bias (MB) in clinical epidemiology (CE) (box 8)

Example of gender bias measuring the delay between the onset of symptoms and obtaining treatment

Gender bias has been proved to be related to the inequitable access, use and quality of healthcare services in men and women with equal needs. Some studies on cardiology therapy and on the management of patients with chest pain, acute myocardial infarction or unstable angina measure sex differences by the time that passes between the onset of symptoms and the request for health assistance given to women compared to men with the same needs remain unclear and support the claim that a professional gender bias may exist.40 The IBERICA study on myocardial infarction in Spain, for example, also shows women experience longer delays from the onset of symptoms to management at hospital (120 minutes for men, 153 minutes for women).39

To prevent a possible information bias that may hamper discovering the cause behind the delay between the onset of symptoms and management at the healthcare centre, two different times should be measured: (1) the time lapse between the onset of symptoms and the request for health assistance that depends on the woman and her environment, and (2) the time lapse between the request for assistance and management that depends on the healthcare professionals.

GENDER BIAS IN THE ANALYSIS OF THE RESULTS

In epidemiological research, certain factors are ignored repeatedly. For example, it can be said that exposure to work burden does not occur equally in men and women. In women with children, the number of hours in the workplace does not represent the total work burden to anywhere near the same extent as it would for men. Women in this situation do not rest and recuperate when they are not at work. On the contrary, for some the workplace is a relatively restful location. Also, the healthy worker effect is different in men and women: women are more strongly health selected into paid employment than men. Furthermore, the occupation given at the time of a census or survey will often not have occupied as many person years of a woman’s life as it would for a man of the same age.

When insufficient information is provided in a report to determine the potentially different effects and contributions that sex may have on the research topic, a drastic review of the research design and analysis is needed. Sex is frequently treated in public health as a potentially confounding variable, the effects of which, if any, are controlled statistically and then ignored. Accordingly, data should be carefully checked to identify gender differences in health.41

### Table 1 Reference values of ferritin in public and private health centres in Spain

<table>
<thead>
<tr>
<th>Public and private health centres</th>
<th>Reference values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(ng/ml)</td>
</tr>
<tr>
<td>Clinical Laboratory, Cornellá-Barcelona, Catalonia</td>
<td>30–300</td>
</tr>
<tr>
<td>Basurto Hospital, Vasco Country</td>
<td>15–150</td>
</tr>
<tr>
<td>Laboratory Echevarne, Granada, Andalusia</td>
<td>10–204</td>
</tr>
<tr>
<td>San Juan de Dios Hospital, Barcelona, Catalonia</td>
<td>10–120</td>
</tr>
<tr>
<td>La Plana Hospital, Vila-Real Valencian Community</td>
<td>5–150</td>
</tr>
<tr>
<td>Unilabs, Barcelona, Catalonia</td>
<td>5–140</td>
</tr>
<tr>
<td>Hermanos Miralles Primary Care Centre, Madrid</td>
<td>14–150</td>
</tr>
<tr>
<td>Folguera Laboratory, Barcelona, Catalonia</td>
<td>15–150</td>
</tr>
<tr>
<td>Fornells, Olè, Creus Laboratory, Barcelona, Catalonia</td>
<td>20–200</td>
</tr>
</tbody>
</table>

### Table 2 Multivariate odds ratios (OR) and 95% confidence intervals (CI) for the associations between self perceived health status and independent variables (Catalonia Health Survey, 1994)

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1</td>
</tr>
<tr>
<td>Women</td>
<td>1.67 (1.37 to 2.03)</td>
</tr>
<tr>
<td>Occupational social class</td>
<td></td>
</tr>
<tr>
<td>Non-manual</td>
<td>1</td>
</tr>
<tr>
<td>Manual</td>
<td>2.00 (1.66 to 2.42)</td>
</tr>
<tr>
<td>Household size</td>
<td></td>
</tr>
<tr>
<td>Two</td>
<td>1</td>
</tr>
<tr>
<td>Three</td>
<td>1.08 (0.75 to 1.55)</td>
</tr>
<tr>
<td>Four</td>
<td>1.39 (0.98 to 1.96)</td>
</tr>
<tr>
<td>&gt; Four</td>
<td>1.58 (1.08 to 2.31)</td>
</tr>
<tr>
<td>Living with children under 15</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>0.96 (0.75 to 1.23)</td>
</tr>
<tr>
<td>Living with people older than 65</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>0.72 (0.53 to 0.98)</td>
</tr>
</tbody>
</table>

Odds ratios are also adjusted for age.
Furthermore, interactions between traditional gender roles and emerging situations may influence current trends in gender differences as regards health related behaviours and their impact on health status. The gender perspective must therefore be applied to the knowledge produced on the sex division of reproductive (domestic and caring) and productive work and its impact on health.

In 2001, a study was conducted on workers aged 25–64 who were married or cohabiting (2148 men and 1185 women) to examine the association between family demands and six health indicators. The data were taken from the 1994 Catalonian Health Survey (CHS), a cross-sectional survey based on a representative sample of the non-institutionalised population of Catalonia, a region in north eastern Spain with approximately six million inhabitants. Family demands were measured through three variables: household size, living with children under 15 and living with people older than 65. Multiple logistic regression models and adjusted odds ratios (AOR) were fitted and 95% confidence intervals (CI) were calculated.

Tables 2–4 illustrate why it is important that statistical analyses consider the potential interaction of gender and social class when examining variables associated with self perceived health status. In table 2, sex and occupational social class are introduced as adjusting variables, thereby assuming that the impact of family demands on health is similar for men and women and does not differ by social class. According to these results, the likelihood of reporting a poor self perceived health status increases with household size, whereas living with people older than 65 seems to be protective, regardless of sex and social class.

However, in table 3, the analysis has been stratified by sex and the results change dramatically. Household size and living with people aged over 65 can be seen to be associated only with women’s health. Taking into account that women are still mainly responsible for domestic tasks, even when they are employed, these results seem to adjust better to the theoretical framework.

Resources for dealing with domestic work should be taken into account. It has been reported that hiring a person to do domestic tasks is associated with good self perceived health status among married female workers after adjusting for age and social class. No such association was found among married male workers. In fact, when the analysis is additionally stratified by social class, the impact of family demands, both as regards household size and living with people aged over 65, is limited to women from manual social classes (table 4). Once again, these results are more coherent with the theory. Women belonging to non-manual social classes have more resources for coping with domestic work. High income enables them to pay...
for help with domestic tasks and childcare andrelieves them of some of the overload. Some female manual workers may be helped with domestic tasks by elderly people living at home.

The epidemiological analysis of the interactions of being employed, domestic work, gender and social class is not easy. It has been pointed out that the use of interaction terms in regression models is as adequate as stratified analysis and has the advantage of preserving parsimony. However, although this position can be defended on statistical grounds, an important part of the theoretical richness and intuitive interpretation is lost. Moreover, given the gendered nature of almost all aspects of social life, many interaction terms (some of which have more than two variables) are required in statistical models; thus making it difficult to interpret results.44

EPIDEMIOLOGICAL GENDER BIAS IN SPECIFIC WOMEN’S HEALTH PROBLEMS

Examples of bias in research on violence against women

From a gender perspective, many health problems are manifestations of the asymmetrical relations of power (inequality and dominance) between men and women. This applies to intimate partner violence (IPV) against women. Because of this, the Ethics Code for Violence Research advises that women should not be exposed to risk situations even if bias is produced in research.

A selection bias was found in a cross-sectional study carried out in 23 primary health centres in Spain, which quantified IPV prevalence and measured its physical and psychological impact out in 23 primary health centres in Spain, which quantified IPV should not be exposed to risk situations even if bias is produced in research.

The following case involves a study on the effects of exposure to pesticides on reproduction and illustrates how gender stereotypes may influence a biased perception of risk, making it necessary to re-analyse the information in order to identify the risks existing in women population groups that had not initially been classified as risk groups.45

When working women were compared to housewives to evaluate the effects on reproduction, worse results were observed in the housewives: low birth weight relative risk (RR) = 1.2 (1.1 to 1.3) and preterm delivery RR = 1.2 (1.1 to 1.4).46 The possible reasons for these results are a healthy worker selection bias, differences in access to medical care during pregnancy and differences in other risk factors that could aggravate the situation. However, another explanation could be misclassification bias. Housewives could sometimes be classified as unexposed to a risk when in fact they were exposed. For instance, the great risk of fetal mortality in children of agricultural workers exposed to pesticides was RR = 1.62 (1.01 to 2.60). However, when this RR was stratified by the occupational status of the wives of agricultural workers exposed to pesticides (housewives vs employed women), it was higher for housewives, RR = 1.68 (1.03 to 2.73), and lower for employed women, RR = 1.24 (0.38 to 4.02).47 These results may be due to indirect exposure (washing laundry, longer time spent at home, etc) or to the fact that the housewives may have helped their partners apply the pesticides.

CONCLUSIONS

This paper has presented a framework to show how systematic errors involving gender influence research findings. This framework has a limited structure and has been elaborated to stimulate debate in the complex area of gender and health research. Conceptual and methodological gender bias produces partial and/or invalid knowledge that affects women’s health.

Gender bias is related to a general social construct, to the way researchers conceive a study, to the accuracy of results and to how these results are used to inform healthcare policy makers, as well as health care, preventive and health promotion services.

Identifying an objective and measurable bias in the management of health problems is an important aim of those researchers working in evidence based medicine and public health. Based on their experience, medical and public health professionals may be able to provide helpful hypotheses related to forms of gender bias that may occur in clinical and social research on health problems that affect both sexes or on specific women’s health issues.
REFERENCES