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Sex Bias in Studies Selected for Clinical Guidelines

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Abstract

Objective: To determine the proportions of female participants in research studies selected to inform the development of national clinical guidelines and to assess these against the proportions of women affected by the conditions.

Methods: We assessed 392 published articles, involving a total of 5.2 million participants, cited as references in five influential clinical guidelines addressing the use of antiarrhythmics, chronic fatigue, depression, diabetes, and colorectal cancer. For each article, we extracted the number of female participants to determine any discrepancies in the sex of participants and if the proportion of female participants as research subjects reflected the sex distribution of patients affected by the condition.

Results: The overall and median percentages (per study) of females per guideline were: use of antiarrhythmics (35%, median 38%), chronic fatigue (70%, median 73%), colorectal cancer (67%, median 46%), depression (66%, median 66%), and diabetes (63%, median 50%). The baseline prevalence rates used for comparison purposes were (percentage female): antiarrhythmics (60% of patients 75^{+} years); chronic fatigue (66%), colorectal cancer (46%), depression (66%), and diabetes (46%).

Conclusions: The colorectal cancer, depression, and chronic fatigue guidelines were based on research populations that accurately reflected the sex distribution of the condition in the general population. Women were slightly overrepresented in the research studies supporting the diabetes guidelines and were significantly underrepresented in the research studies supporting the guidelines on the use of antiarrhythmics. Guideline developers should be aware of and comment on the potential impact of sex. Where the evidence base is lacking, guideline developers should highlight this and, where necessary, limit their specific conclusions to populations on whom the research was performed.

Introduction

There are important differences between males and females due to both biologic (sex) and social (gender) factors in the incidence, treatment responses, and prognosis of a range of diseases.[1] Cardiovascular disease (CVD) is a widely recognized example,[2] but sex differences also exist in a range of diseases, including arthritis, depression, and tropical and infectious diseases.[3,4] In order to provide optimal care, sex and gender differences should be systematically considered and addressed in clinical research and evidence-based clinical guidelines.

The history of medical research reveals the exclusion of women and ethnic minorities from many important research trials. The findings from studies conducted on white middle-aged men were extrapolated to, and formed the basis of, clinical treatment for women, the elderly (often with various comorbidities), and alternative ethnic groups. The result is that "medicine as it is currently applied to women is less evidence-based than that being applied to men."[5] In recognitions of this sex bias, many countries introduced policy or regulatory measures to encourage greater recruitment of women in clinical trials during the 1990s and 2000s.[6–8]

Reviews have been conducted by government agencies and independent researchers, particularly in Canada, the United States, and Australia, to determine the success of these state interventions. In general, these reviews indicate increased rates of inclusion of women in research. Recent reviews have found that women, on average, now represent the majority of research participants.[1,9] However, unjustified sex biases remain: men are considerably more likely to be recruited for non sex-specific research, whereas women are more likely to be recruited for sex-specific research; a high proportion of women's health research continues to focus predominantly on

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their reproductive capacity and function; and women continue to be underrepresented in cardiovascular-related research. Interestingly, a similar pattern occurs in guideline development. Discussion of sex differences in guideline development focuses on reproductive matters (pregnancy and breastfeeding).[10] Reviews of published research show that only 7%–28% of publications include sex-specific reporting or results, and 7%–24% provide statistical analysis of sex differences.[1,11]

The inclusion of women in trials is important because in the age of evidence-based medicine, research trials directly influence clinical practice guidelines and, thus, clinical care. Only a small proportion of the published medical research literature is deemed of sufficient quality to inform clinical guideline development. Therefore, it is possible that clinical studies that unjustifiably or inappropriately exclude males or females are culled on methodologic grounds and not used as the basis for clinical treatment guidelines. To test this hypothesis, we reviewed the references in four influential national guidelines and one Cochrane review to determine the rates of female participation in research informing guideline development. The Cochrane review was included because Cochrane reviews are highly regarded for their methodologic rigor and often form the basis for clinical practice guidelines. Therefore, examination of a Cochrane review provides insight into any potential differences between reviews and guidelines and gives an indication of the extent to which sex differences are entering the methodology that underpins guideline development.

Materials and Methods

The following criteria were used to select five guidelines for investigation: published by nationally recognized health authorities in the United States, Australia, and Britain; addressing treatment for different diseases; involving diseases known to have sex differences; published after 2000. The guidelines and review were selected to reflect a range of diseases for which there are varying degrees of recognition of sex differences.[2,12–15] The following guidelines were selected: Royal College of General Practitioners guidelines on chronic fatigue syndrome (CFS); National Health and Medical Research Council guidelines on type 2 diabetes and colorectal cancer; BeyondBlue guidelines for depression; and Cochrane review of the use of antiarrhythmic medication. Details of the guidelines are presented in Table 1.

We used the reference lists from each guideline to identify the research studies that had been used in the formulation of the guidelines, and we reviewed each of the original research articles. For the Cochrane review of antiarrhythmic medication, we used the data extracted by the reviewers and presented in the table, Characteristics of Studies Included, in the review.[16] For the other four guidelines, all references to original research were included in our analysis; these consisted of clinical research, drug trials, social and behavioral research, and epidemiologic studies. We also included references to meta-analyses where the primary data were reproduced. We excluded references that referred to material other than research reports or meta-analyses of original research. Excluded material included government reports, books, discussion articles, and narrative review articles. We also excluded references not published in English and studies

Table 1. Clinical Guidelines

Short title	*Organization*	*Country*	*Year*	*Full title*	*Section analyzed*
Antiarrhythmic medication	Cochrane	USA	2007	Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation[16]	All
Chronic fatigue syndrome (CFS)	Royal College of General Practitioners (RCGP)	UK	2007	NICE guidelines for the diagnosis and management of chronic fatigue syndrome/ myalgic encephalomyelitis (or encephalopathy) in adults and children.[17]	All
Colorectal cancer	National Health and Medical Research Council (NHMRC)	Australia	2005	Clinical practice guidelines for the prevention, early detection and management of colorectal cancer[18]	Part Two: Primary prevention recommendations
Diabetes	National Health and Medical Research Council (NHMRC)	Australia	2005	National evidence based guidelines for the management of type 2 diabetes mellitus[19]	Part Two: Primary prevention of type 2 diabetes
Depression	BeyondBlue	Australia	2003	Treating depression: The BeyondBlue guidelines for treating depression in primary care[20]	All

NICE, National Institute for Health and Clinical Excellence.

with nonhuman animals. The Cochrane review of antiarrhythmic medication referenced numerous publications based on one study; we included only the data from the reference identified as the major study by the Cochrane reviewers.

For each reference included in our analysis, we recorded the type of study (female-only, male-only, or mixed sex participants), total number of participants, and number of male and female participants, using Microsoft Excel. We calculated the percentage of female participants per study and the mean and median percentages of female participants in the references per selected guideline. Where the guideline was arranged according to specific clinical practice recommendations, we also calculated the mean and median percentages of female participants per recommendation.

We then compared the proportions of sex of participants in the studies to the sex of patients affected by each condition. We used various benchmarks to determine if the inclusion rates of women in the studies supporting the guidelines reflected the proportion of female patients affected by the condition. We used nationally compiled country-specific data where possible. For the National Health and Medical Research Council (NHMRC) colorectal cancer and diabetes guidelines, we used data from The Burden of Disease and Injury in Australia 2003.[21] For the BeyondBlue depression guidelines, we used the most recent global burden of disease statistics, compiled by the World Health Organization (WHO).[22] Atrial fibrillation (AF) and CFS are not included in the global burden of disease report, so published articles[23–28] were used to establish population distributions for these conditions.

Results

From the five guidelines, we included a total of 392 articles and excluded 66 articles. Articles in the resulting dataset were published between 1970 and 2006 and included >5.2 million participants. The results are presented per guideline and summarized in Table 2. The two NHMRC guidelines on diabetes and colorectal cancer have the evidence arranged according to specific clinical practice recommendations, and the data on participation rates for these two guidelines are summarized by recommendation in Tables 3 and 4.

Antiarrhythmics

The Cochrane antiarrhythmics review[16] was based on data from 45 articles. One unpublished article did not record the sex of participants. Data from the remaining 44 studies, published between 1970 and 2005, are included in our analysis. A total of 11,312 participants were included in these studies. Overall, 35% of the participants were female; both the mean and median percentages of females were 38%.

Chronic fatigue syndrome

We excluded 34 of 51 references in the Royal College of General Practitioners (RCGP) CSF guidelines.[17] Most excluded articles were narratives or reports. Seventeen articles, published between 1992 and 2006, were analyzed, and these included 1,689 participants. Overall, 70% of the participants were female; the mean percentage of females was 74% and the median was 73%. There was only one sex-specific study that involved females.

Table 2. Number and Percentage of Male and Female Participants per Guideline

			Sex not recorded	*Sex recorded*								
Guideline	*References excluded*	*References included*	*(No. of studies participants)*	*Male only*	*Female only*	*Male and female*	*No. of participants*	*No. of male participants*	*No. of female participants*	*% female participants*[a]	*Mean % female*[b]	*SD*	*Median % female*[c]
Antiarrhymics	0	45	1 (1,227)	0	0	44	11,312	7,380	3,932	35	38	14	38
Chronic fatigue	34	17	3 (2,981)	0	1	13	1,689	509	1,180	70	74	14	73
Colorectal cancer	27	58	2 (490,251)	3	12	41	4,096,647	1,351,951	2,744,696	67	54	29	46
Depression	1	105	8 (1,566)	0	0	97	15,875	5,442	10,433	66	64	12	66
Type 2 diabetes	4	166	11 (31,197)	38	42	86	1,089,051	398,764	690,287	63	53	38	50

[a]Number of female participants divided by total number of participants in all studies where the sex of participants was recorded.
[b]Mean was calculated by adding all the percentages of female participants in each of the studies where the sex of participants was recorded and dividing this by the number of studies were sex was recorded.
[c]Median was calculated by listing the percentages of female participants in each of the studies where the sex of participants was recorded and identifying the middle number.
SD, standard deviation.

Table 3. Number and Percentage of Male and Female Participants per Recommendation in Colorectal Cancer Guidelines

Recommendation	References excluded	References included	Sex not recorded: Studies (no. of participants)	Sex recorded: Male only	Female only	Male and female	No. of participants	No. of male participants	No. of female participants	% female participants[a]	Median % female[b]
1. Engage in moderate to vigorous physical activity for 30–60 minutes/day and avoid excessive weight gain	3	3	0	1	0	2	34,894	32,319	2,575	7	44
2. Weight should be maintained in the healthy weight range of BMI	4	4	0	1	2	1	1,012,398	405,379	607,019	60	78
3. Alcohol consumption should be limited or avoided; for people who do drink alcohol, recommended amounts for men are no more than 2 standard drinks per day and for women no more than one standard drink per day	1	5	1 (489,979)	0	1	3	120,681	16,746	103,935	86	46
4. Avoid tobacco smoking	2	3	0	0	1	2	825,175	313,514	511,661	62	60
5. Limit energy intake in most men to <2,500 calories (10,480 kJ) per day and in most women to <2,000 calories (8,360 kJ) per day	1	2	0	0	1	1	101,714	6,891	94,823	93	73
6. Reduce dietary fat to <25% of calories as fat	2	6	0	0	1	5	127,942	18,476	109,466	86	46
7. Moderate intakes of lean red meat can be eaten as part of a mixed diet including carbohydrates (breads and cereals), vegetables and fruit, and dairy products; charring of red meat is best avoided; consumption of processed meats should be limited	3	3	0	0	1	2	567,185	142,252	424,933	75	70
8. Eat five or more servings per day of a variety of vegetables; national nutrition guidelines also advise two servings of fruit daily ("Go for 2 and 5")	1	6	0	0	1	5	541,481	144,204	397,277	73	45
9. Select poorly soluble cereal fibers (e.g., wheat bran), especially if at increased risk for colorectal cancer	3	4	0	0	0	4	38,223	19,896	18,327	48	44
10. Ensure a total calcium intake of 1,000–1,200 mg/day in keeping with general dietary guidelines	1	4	0	0	0	4	545,684	208,729	336,955	62	59
11. Selenium supplementation for chemoprevention is promising but requires confirmation	1	3	0	0	0	3	1,927	1,476	451	23	25
12. Antioxidant vitamin supplementation is not advised at present to protect against colorectal cancer	1	4	0	0	0	4	1,389	999	390	28	34
13. Aspirin should be considered as prophylaxis against further adenoma development in those with previous removal of an adenoma	3	7	1 (272)	1	1	4	81,816	38,959	42,857	52	47
14. HRT cannot be recommended as prophylaxis against colorectal cancer because of its possible collateral risks, including breast cancer	1	4	0	0	3	1	96,138	2,111	94,027	98	100

[a]Number of female participants divided by total number of participants, included in all studies where the sex of participants was recorded.
[b]Median was calculated by listing the percentages of female participants in each of the studies where the sex of participants was recorded and identifying the middle number.
BMI, body mass index; HRT, hormone replacement therapy.

Table 4. Number and Percentage of Male and Female Participants per Recommendation in Diabetes Guidelines

Recommendation	References Excluded	References included	Sex not recorded	Sex recorded							
			Studies (no. of participants)	Male only	Female only	Male and female	No. of participants	No. of male participants	No. of female participants	% female participants[a]	Median % female[b]
1. Since obesity is associated with an increased risk of type 2 diabetes, interventions to reduce obesity may reduce the risk of type 2 diabetes	0	24	4 (4,755)	8	2	14	269,802	93,540	176,262	65	48
2. Abdominal obesity is an important indicator of increased risk of type 2 diabetes in all ethnic groups and should be a particular focus of weight loss programs	0	22	1 (721)	6	5	11	132,414	70,597	61,817	47	56
3. Waist circumfrence should be used in addition to BMI to identify individuals who should seek and be offered weight management programs	0	11	0	2	2	7	122,762	64,723	58,039	47	51
4. Regular physical activity is recommended to reduce the risk of type 2 diabtetes	0	15	0	8	1	6	160,719	68,089	92,630	58	0
5. Physical activity should be measured in free-living subjects by movement recorders, particularly the pedometer, questionnaires focusing on leisure time activities, heart rate monitoring; functional aerobic capacity should be measured from predictive equations based on gender, age, self-reported physical activity, and body composition or BMI	0	16	2 (36)	3	3	10	4,699	3,900	799	17	38
6. Individuals at risk of developing type 2 diabetes should have dietary intake assessed and should receive individualized dietary advice and continued dietetic support; individuals at risk should consume a diet with <30% energy as fat, with <10% as saturated fat	0	14	1 (666)	2	3	9	94,329	4,197	90,132	96	58
7. Identification of women with GDM would allow postnatal clinical interventions in those with diabetes persisting after delivery, the option to use preventive methods to reduce the risk of type 2 diabetes	0	16	0	0	14	2	60,735	605	60,130	99	100
8. In view of the association between low birth weight and later development of diabetes, studies are required to evaluate	1	15	0	5	5	5	98,713	26,547	72,166	73	49

(*continued*)

Table 4. (Continued)

Recommendation	References Excluded	References included	Sex not recorded	Sex recorded							
			Studies (no. of participants)	Male only	Female only	Male and female	No. of participants	No. of male participants	No. of female participants	% female participants[a]	Median % female[b]
interventions aimed at reducing low birth weight and the impact this has on the development of type 2 diabetes											
9. Diets of low energy density and containing a wide range of carbohydrate foods rich in dietary fiber and of low glycemic index (cereals, vegetables, legumes and fruits) are recommended to reduce the risk of type 2 diabetes	0	2	0	1	1	0	107,932	42,759	65,173	60	50
10. More research is required to assess the impact of psychologic stress or a major depressive episode in affecting the risk of type 2 diabetes	0	9	1 (25,019)	1	0	8	20,038	12,610	7,428	37	50
11. Programs of diet and exercise education in children should include parental involvement and use behavioral techniques to reinforce lifestyle change	3	22	2 (81)	2	6	14	16,908	11,197	5,711	34	71

[a]Number of female participants divided by total number of participants included in all studies where the sex of participants was recorded.
[b]Median was calculated by listing the percentages of female participants in each of the studies where the sex of participants was recorded and identifying the middle number.
GDM, gestational diabetes mellitus.

Colorectal cancer

From the NHMRC colorectal cancer guidelines,[18] we excluded 27 references. Fifty-eight articles, published between 1987 and 2005, were included in our analysis (Table 3). Two of these articles, including 490,251 participants, did not record the research subjects' sex. The remaining 56 articles included a total of 4.1 million participants. Overall, 67% of the participants were female; the mean percentage of females was 54% and the median was 46%. Only 5% of studies were male-only, whereas 21% of studies included female-only populations. The substantial difference between the median (46%) and overall (67%) percentage of females is due to the large number of female-only studies.

In relation to specific recommendations, Recommendation 1 addresses physical activity; the research underpinning this recommendation is based on studies with 93% males (median percentage of females across the three studies was 44%). In contrast, Recommendations 2, 5, and 6, which deal with weight and calorie control, are based on studies that have 59%, 93%, and 85% females (with respective medians of 78%, 73%, and 46% females).

Depression

The BeyondBlue depression guidelines[20] were based on 106 references, of which 105, published between 1984 and 2001, are included in our analysis. Eight studies did not record the sex of participants; this represented 9.9% of the overall participants. The remaining 97 studies included a total of 15,875 participants, and all studies included both males and females. Overall, 64% of the participants were female; the mean percentage of females was 64% and the median was 66%.

Type 2 diabetes

From the NHMRC diabetes guidelines,[19] we excluded 4 references and based our analysis on the remaining 166 articles published between 1973 and 2002 (Table 4). Eleven articles, including 31,197 participants, did not record the participants' sex. The remaining 155 studies included 1.1 million participants. Overall, 63% of the participants were female; the mean percentage of females was 53% and the median was 50%. Interestingly, the diabetes studies included a much higher proportion of sex-specific studies than did the other guidelines; 23% of studies were male-only, and 25% were female-only.

As with the colorectal cancer guidelines,[18] there were specific recommendations in the diabetes guidelines about exercise.[19] Recommendation 1 relates to physical activity and is broken down further into eight specific recommendations. Of these, four apply to both men and women; three of these are based on research with both men and women, whereas one is based on evidence derived from males only. The remaining four exercise-related recommendations are for men only, based on research with males.

Appropriate representation of women in the selected evidence base

The final part of the analysis compared the rates of participation of women in the guidelines reviewed here with the proportions of women affected by the condition.

Antiarrhythmics

Women represented 35% of the overall research participants (median 38% across the 44 studies). The clinical picture of AF is complex, so we explain here the age-related incidence of AF in order to contextualize the results. The median age of patients with AF is 75 years,[23] and the diagnosed rate of AF is 5% in women and 7.3% in men at 75–79 years. The actual population rate (both diagnosed and undiagnosed) has been measured in patients 85+ and is 12.1% in women and 16.6% in men.[24] Because of women's increased life span, they account for 60% of patients aged 75+ with AF in the United States.[25] The risk of stroke and mortality associated with AF is significantly higher in women.[25] There is an important interaction among age, stroke risk, and sex, with female AF patients >age 75 at particularly high risk for stroke.[23] Prevalent AF has been associated with a 50% excess in all-cause mortality in men compared to a 90% excess in women.[26] The proportion of women in AF research in this review does not reflect the population incidence or the impact of AF on women's health.

Chronic fatigue syndrome

Clinical studies can show a ratio of up to 1:4 male/female CFS patients.[27] However, population studies indicate that the rate of CFS among males is higher and suggest a ratio of 1:2.[28] It is possible that women are more likely than men to seek clinical treatment for CFS. Of the participants in the studies we analyzed, 70% were female, which reflects the estimated population ratio of 1:2.

Colorectal cancer

Australian Institute for Health and Welfare (AIHW) data show that Australian women suffer from 46% of the annual 63,605 disability adjusted life years (DALYs) lost to colon and rectal cancer and also 46% of the annual 4,871 deaths.[21] Measured against this baseline, women were overrepresented in the evidence supporting the NHMRC colorectal guidelines,[18] representing 67% of the overall research participants. However, the mean was influenced by a large number of female-only studies. The median percent female participants across the studies was 46%, which more accurately reflects the sex distribution in the patient population.

Depression

Women are more affected by unipolar depression (UPD) than men, accounting for two thirds of the global annual 65 million DALYs and half the suicide rate associated with UPD in 2004.[22] The greater proportion of female participants in the BeyondBlue depression-related studies[20] (66% female) accurately reflects the population affected by this condition.

Type 2 diabetes

In Australia, women account for 46% of the 132,940 DALYs lost to type 2 diabetes and also 46% of the 3,130 deaths resulting from type 2 diabetes each year.[21] Women, at 63% of the research participants, were therefore overrepresented in the diabetes research studies referenced by the NHMRC diabetes guidelines.[19]

Discussion

To our knowledge, this is the first study to review the inclusion of women in research used to develop an international selection of clinical practice guidelines. Two prior studies conducted in the Netherlands focused on sex-related factors in the development of Dutch clinical guidelines.[29,30] These showed that the authors of the guidelines did not pay special attention to sex-related differences when developing the guidelines[29] and that the number of sex-specific recommendations ranged from 0 of 148 recommendations in depression guidelines to 16 of 84 recommendations in osteoporosis guidelines.[30] Keuken et al.[29] concluded that the lack of sex-related evidence in the published literature is a major contributory factor to the lack of sex-specific recommendations in guideline documents. Melloni et al.[31] used the 2007 American Heart Association guidelines to identify randomized controlled trials (RCTs) in their investigation of female participation rates in RCTs of CVD prevention; they found underrepresentation of women in these trials.

Cardiovascular research

Exclusion of women from cardiovascular research has been one of the widely discussed examples of the underrepresentation of women in clinical research and is thought to contribute to the undertreatment of CVD in women.[32] We, therefore, expected higher rates of female participation in the evidence base for this review addressing the use of antiarrhythmics.

The US National Institutes of Health (NIH) Revitalization Act[6] came into force in 1993, requiring appropriate inclusion of women in publicly funded clinical research. Twenty-eight of the 38 antiarrhythmics articles (74%) were published after 1993; however, many of the studies would already have enrolled participants before the regulatory change. However, 20 of 38 (53%) articles were published in or after 2000, by which time one would expect the inclusion rates of women to be increasing both as a direct response to the NIH requirements and indirectly as part of the increased recognition of the need to include women in cardiovascular research. The percentage of women in these studies is no greater than in the full dataset. In the 20 studies published after 2000, the range of percentage of women is 1%–51%, the median percentage of women was 36%, and only 33% of the 8,188 participants in these studies were female. This result suggests persistent bias against the inclusion of women in cardiovascular research.

The study including only 1% female participation was conducted by the SAFE-T 2000 research group[33] and involved 665 patients recruited from Veterans Affairs organizations in the United States. The recruitment strategy clearly explains the overwhelming proportion of male participants, but the authors do not address this as a limitation of the study, restrict their conclusions to male patients, or discuss the potential role of sex as a variable in the effectiveness of amiodarone vs. sotalol for atrial fibrillation. Yet a study has shown the risk of bradyarrhythmia requiring pacemaker insertion associated with amiodarone use for AF is significantly greater in women than in men, independent of weight or body mass index.[34]

Given the clinical picture of AF, it is disturbing that AF-related evidence-based guidelines are based on research conducted primarily with males. Our findings support previous reviews showing that contemporary guidelines for prevention, diagnostic testing and medical and surgical treatments for CVD are still based on studies conducted predominantly with men.[31,35]

Gender stereotypes relating to diet and exercise

Recommendations within the colorectal cancer and diabetes guidelines reflected gender stereotyping. Women formed the majority of participants in research for diet-related recommendations, and this was not noted in the guideline. In relation to exercise, the diabetes guideline developers noted the sex of research participants in the majority of cases, leading to a predominance of male-only recommendations that accurately, if uncritically, reflects the comparative lack of research into the effects of exercise in women.

The small sample sizes considered here provide insufficient data to show systematic stereotyping. However, the data correlate with previous findings showing gender stereotyping in sex-specific injury prevention studies, where studies with men recruited athletes and focused on peak performance, whereas studies with women focused on prevention of falls among the elderly.[36]

Analysis of sex differences

The conditions we considered all have recognized sex differences, yet sex and gender were rarely discussed in the body of the guidelines. In the two reports where women were overrepresented or underrepresented in the research population, there was no acknowledgment of this as a limitation of the research base or on the applicability of the guidelines to the wider population. Sex and gender factors were not discussed in the antiarrhythmic guidelines.[16] The underrepresentation of women in the research base is not mentioned in the section addressing risk of bias in included studies. Subgroup analysis by sex was not conducted.

The CFS guidelines[17] discussed sex differences, stating that CFS affects women at approximately four times the rate of men. This refers to the clinical ratio (1:4) rather than the estimated population ratio (1:2). Relative to the clinical ratio, women are underrepresented in the research base supporting these guidelines (70% female), but this is not mentioned by the reviewers. There are no other substantive references to sex or gender. (The only additional sex-related comments were in relation to 2 studies that were excluded from the analysis. It is unclear whether the studies were partially excluded because they were female-only populations or the sex of the research participants was incidental.)

The colorectal cancer guidelines[18] include 13 recommendations in Chapter 2 regarding primary prevention of colorectal cancer; 3 of these include sex-specific comments. The literature base supporting each recommendation is discussed, and the varying applicability of results to men and women is mentioned in relation to physical exercise, obesity, and alcohol consumption. Recommendation 3 provides sex-specific guidelines for limiting energy intake in men and women, but the discussion does not mention that 93% of the overall research population referenced was women. Selenium and antioxidant vitamin supplementation (recommendations 11 and 12) were based on research with approximately 75% males, but this was not noted by the reviewers.

There is no discussion about the impact of sex or gender in the BeyondBlue depression guidelines.[20] The recommendations

are organized according to the type of depression (mild, moderate, or severe) and the presence of other relevant comorbidities.

The NHMRC type 2 diabetes guidelines[19] state that the recommendations should be used only as a guide and applied to individual patients with caution to assist clinical decision making. The individual recommendations in this guideline use various qualifiers including people, men and women, men only, and women only, or have no qualifier. In some cases, for example, in relation to the evidence statement that: "In both men and women, physical activity reduces the risk of type 2 diabetes," there is acknowledgment that women have been less well studied on this topic. In other cases, for example, the evidence statement: "Weight loss is associated with reduced progression of IGT [impaired glucose tolerance] to Type 2 diabetes," most of the data are from research with women, but there is no sex qualifier on the advice. The role of sex is not discussed in any detail, apart from a discrete section in the guidelines that deals with gestational diabetes.

Limitations of our study

Our study has several limitations. First, because of the time-consuming methodology, we were able to analyze only a small number of the many evidence-based guidelines available. Second, our methodology had to be adapted to the specific review processes of each guideline, which limits the comparability of the results across the guidelines. For example, the NHMRC guidelines are organized into specific recommendation. A single study could be used to support multiple recommendations and was, therefore, counted multiple times in our analysis. In contrast, the Cochrane review indicated when multiple articles referred to the same study and identified the major study; in our analysis, we included only the major study and can be confident that research populations were not counted more than once. Third, we have not systematically coded the text of the guidelines or cross-referenced the text to the supporting research to determine if all clinical recommendations are appropriately supported by research with both sexes. However, we did conduct an analysis of the NHMRC colorectal cancer and diabetes guidelines because these documents were organized according to specific recommendations.

Conclusions

Clinical guidelines do not always or consistently take account of the sex of participants in research. Whereas three of the guidelines that we studied were based on research populations that accurately reflected the sex distribution of the condition in the general population, women were overrepresented in the diabetes guidelines and significantly underrepresented in the antiarrhythmic guidelines. In addition, there was varying attention to sex differences, with examples of recommendations for both sexes based on research with one sex, often without clarification or qualification. Sex-specific recommendations relating to exercise uncritically reproduced gender stereotyping.

We support the recent Institute of Medicine recommendation that journals require reporting data on men and women separately and provide sex-specific analyses for all publications.[37] This will oblige researchers to design studies that can provide separate and independent answers for men and women. Guideline developers are dependant on the research evidence available, but they are also responsible for how they frame their questions and analyze the evidence. Guideline developers should ask separate questions about the health of men and women and explicitly look for evidence to answer these questions. In the absence of sex-specific evidence, recommendations should be suitably qualified in order to inform practice and guide future research.

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Sex Bias in Studies Selected for Clinical Guidelines

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Abstract

Objective: To determine the proportions of female participants in research studies selected to inform the development of national clinical guidelines and to assess these against the proportions of women affected by the conditions.

Methods: We assessed 392 published articles, involving a total of 5.2 million participants, cited as references in five influential clinical guidelines addressing the use of antiarrhythmics, chronic fatigue, depression, diabetes, and colorectal cancer. For each article, we extracted the number of female participants to determine any discrepancies in the sex of participants and if the proportion of female participants as research subjects reflected the sex distribution of patients affected by the condition.

Results: The overall and median percentages (per study) of females per guideline were: use of antiarrhythmics (35%, median 38%), chronic fatigue (70%, median 73%), colorectal cancer (67%, median 46%), depression (66%, median 66%), and diabetes (63%, median 50%). The baseline prevalence rates used for comparison purposes were (percentage female): antiarrhythmics (60% of patients 75^{+} years); chronic fatigue (66%), colorectal cancer (46%), depression (66%), and diabetes (46%).

Conclusions: The colorectal cancer, depression, and chronic fatigue guidelines were based on research populations that accurately reflected the sex distribution of the condition in the general population. Women were slightly overrepresented in the research studies supporting the diabetes guidelines and were significantly underrepresented in the research studies supporting the guidelines on the use of antiarrhythmics. Guideline developers should be aware of and comment on the potential impact of sex. Where the evidence base is lacking, guideline developers should highlight this and, where necessary, limit their specific conclusions to populations on whom the research was performed.

Introduction

There are important differences between males and females due to both biologic (sex) and social (gender) factors in the incidence, treatment responses, and prognosis of a range of diseases.[1] Cardiovascular disease (CVD) is a widely recognized example,[2] but sex differences also exist in a range of diseases, including arthritis, depression, and tropical and infectious diseases.[3,4] In order to provide optimal care, sex and gender differences should be systematically considered and addressed in clinical research and evidence-based clinical guidelines.

The history of medical research reveals the exclusion of women and ethnic minorities from many important research trials. The findings from studies conducted on white middle-aged men were extrapolated to, and formed the basis of, clinical treatment for women, the elderly (often with various comorbidities), and alternative ethnic groups. The result is that "medicine as it is currently applied to women is less evidence-based than that being applied to men."[5] In recognitions of this sex bias, many countries introduced policy or regulatory measures to encourage greater recruitment of women in clinical trials during the 1990s and 2000s.[6–8]

Reviews have been conducted by government agencies and independent researchers, particularly in Canada, the United States, and Australia, to determine the success of these state interventions. In general, these reviews indicate increased rates of inclusion of women in research. Recent reviews have found that women, on average, now represent the majority of research participants.[1,9] However, unjustified sex biases remain: men are considerably more likely to be recruited for non sex-specific research, whereas women are more likely to be recruited for sex-specific research; a high proportion of women's health research continues to focus predominantly on

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their reproductive capacity and function; and women continue to be underrepresented in cardiovascular-related research. Interestingly, a similar pattern occurs in guideline development. Discussion of sex differences in guideline development focuses on reproductive matters (pregnancy and breastfeeding).[10] Reviews of published research show that only 7%–28% of publications include sex-specific reporting or results, and 7%–24% provide statistical analysis of sex differences.[1,11]

The inclusion of women in trials is important because in the age of evidence-based medicine, research trials directly influence clinical practice guidelines and, thus, clinical care. Only a small proportion of the published medical research literature is deemed of sufficient quality to inform clinical guideline development. Therefore, it is possible that clinical studies that unjustifiably or inappropriately exclude males or females are culled on methodologic grounds and not used as the basis for clinical treatment guidelines. To test this hypothesis, we reviewed the references in four influential national guidelines and one Cochrane review to determine the rates of female participation in research informing guideline development. The Cochrane review was included because Cochrane reviews are highly regarded for their methodologic rigor and often form the basis for clinical practice guidelines. Therefore, examination of a Cochrane review provides insight into any potential differences between reviews and guidelines and gives an indication of the extent to which sex differences are entering the methodology that underpins guideline development.

Materials and Methods

The following criteria were used to select five guidelines for investigation: published by nationally recognized health authorities in the United States, Australia, and Britain; addressing treatment for different diseases; involving diseases known to have sex differences; published after 2000. The guidelines and review were selected to reflect a range of diseases for which there are varying degrees of recognition of sex differences.[2,12–15] The following guidelines were selected: Royal College of General Practitioners guidelines on chronic fatigue syndrome (CFS); National Health and Medical Research Council guidelines on type 2 diabetes and colorectal cancer; BeyondBlue guidelines for depression; and Cochrane review of the use of antiarrhythmic medication. Details of the guidelines are presented in Table 1.

We used the reference lists from each guideline to identify the research studies that had been used in the formulation of the guidelines, and we reviewed each of the original research articles. For the Cochrane review of antiarrhythmic medication, we used the data extracted by the reviewers and presented in the table, Characteristics of Studies Included, in the review.[16] For the other four guidelines, all references to original research were included in our analysis; these consisted of clinical research, drug trials, social and behavioral research, and epidemiologic studies. We also included references to meta-analyses where the primary data were reproduced. We excluded references that referred to material other than research reports or meta-analyses of original research. Excluded material included government reports, books, discussion articles, and narrative review articles. We also excluded references not published in English and studies

Table 1. Clinical Guidelines

Short title	*Organization*	*Country*	*Year*	*Full title*	*Section analyzed*
Antiarrhythmic medication	Cochrane	USA	2007	Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation[16]	All
Chronic fatigue syndrome (CFS)	Royal College of General Practitioners (RCGP)	UK	2007	NICE guidelines for the diagnosis and management of chronic fatigue syndrome/ myalgic encephalomyelitis (or encephalopathy) in adults and children.[17]	All
Colorectal cancer	National Health and Medical Research Council (NHMRC)	Australia	2005	Clinical practice guidelines for the prevention, early detection and management of colorectal cancer[18]	Part Two: Primary prevention recommendations
Diabetes	National Health and Medical Research Council (NHMRC)	Australia	2005	National evidence based guidelines for the management of type 2 diabetes mellitus[19]	Part Two: Primary prevention of type 2 diabetes
Depression	BeyondBlue	Australia	2003	Treating depression: The BeyondBlue guidelines for treating depression in primary care[20]	All

NICE, National Institute for Health and Clinical Excellence.

with nonhuman animals. The Cochrane review of antiarrhythmic medication referenced numerous publications based on one study; we included only the data from the reference identified as the major study by the Cochrane reviewers.

For each reference included in our analysis, we recorded the type of study (female-only, male-only, or mixed sex participants), total number of participants, and number of male and female participants, using Microsoft Excel. We calculated the percentage of female participants per study and the mean and median percentages of female participants in the references per selected guideline. Where the guideline was arranged according to specific clinical practice recommendations, we also calculated the mean and median percentages of female participants per recommendation.

We then compared the proportions of sex of participants in the studies to the sex of patients affected by each condition. We used various benchmarks to determine if the inclusion rates of women in the studies supporting the guidelines reflected the proportion of female patients affected by the condition. We used nationally compiled country-specific data where possible. For the National Health and Medical Research Council (NHMRC) colorectal cancer and diabetes guidelines, we used data from The Burden of Disease and Injury in Australia 2003.[21] For the BeyondBlue depression guidelines, we used the most recent global burden of disease statistics, compiled by the World Health Organization (WHO).[22] Atrial fibrillation (AF) and CFS are not included in the global burden of disease report, so published articles[23–28] were used to establish population distributions for these conditions.

Results

From the five guidelines, we included a total of 392 articles and excluded 66 articles. Articles in the resulting dataset were published between 1970 and 2006 and included >5.2 million participants. The results are presented per guideline and summarized in Table 2. The two NHMRC guidelines on diabetes and colorectal cancer have the evidence arranged according to specific clinical practice recommendations, and the data on participation rates for these two guidelines are summarized by recommendation in Tables 3 and 4.

Antiarrhythmics

The Cochrane antiarrhythmics review[16] was based on data from 45 articles. One unpublished article did not record the sex of participants. Data from the remaining 44 studies, published between 1970 and 2005, are included in our analysis. A total of 11,312 participants were included in these studies. Overall, 35% of the participants were female; both the mean and median percentages of females were 38%.

Chronic fatigue syndrome

We excluded 34 of 51 references in the Royal College of General Practitioners (RCGP) CSF guidelines.[17] Most excluded articles were narratives or reports. Seventeen articles, published between 1992 and 2006, were analyzed, and these included 1,689 participants. Overall, 70% of the participants were female; the mean percentage of females was 74% and the median was 73%. There was only one sex-specific study that involved females.

Table 2. Number and Percentage of Male and Female Participants per Guideline

			Sex not recorded	*Sex recorded*								
Guideline	*References excluded*	*References included*	*(No. of studies participants)*	*Male only*	*Female only*	*Male and female*	*No. of participants*	*No. of male participants*	*No. of female participants*	*% female participants*[a]	*Mean % female*[b]	*SD*	*Median % female*[c]
Antiarrhymics	0	45	1 (1,227)	0	0	44	11,312	7,380	3,932	35	38	14	38
Chronic fatigue	34	17	3 (2,981)	0	1	13	1,689	509	1,180	70	74	14	73
Colorectal cancer	27	58	2 (490,251)	3	12	41	4,096,647	1,351,951	2,744,696	67	54	29	46
Depression	1	105	8 (1,566)	0	0	97	15,875	5,442	10,433	66	64	12	66
Type 2 diabetes	4	166	11 (31,197)	38	42	86	1,089,051	398,764	690,287	63	53	38	50

[a]Number of female participants divided by total number of participants in all studies where the sex of participants was recorded.
[b]Mean was calculated by adding all the percentages of female participants in each of the studies where the sex of participants was recorded and dividing this by the number of studies were sex was recorded.
[c]Median was calculated by listing the percentages of female participants in each of the studies where the sex of participants was recorded and identifying the middle number.
SD, standard deviation.

Table 3. Number and Percentage of Male and Female Participants per Recommendation in Colorectal Cancer Guidelines

Recommendation	References excluded	References included	Sex not recorded: Studies (no. of participants)	Sex recorded: Male only	Female only	Male and female	No. of participants	No. of male participants	No. of female participants	% female participants[a]	Median % female[b]
1. Engage in moderate to vigorous physical activity for 30–60 minutes/day and avoid excessive weight gain	3	3	0	1	0	2	34,894	32,319	2,575	7	44
2. Weight should be maintained in the healthy weight range of BMI	4	4	0	1	2	1	1,012,398	405,379	607,019	60	78
3. Alcohol consumption should be limited or avoided; for people who do drink alcohol, recommended amounts for men are no more than 2 standard drinks per day and for women no more than one standard drink per day	1	5	1 (489,979)	0	1	3	120,681	16,746	103,935	86	46
4. Avoid tobacco smoking	2	3	0	0	1	2	825,175	313,514	511,661	62	60
5. Limit energy intake in most men to <2,500 calories (10,480 kJ) per day and in most women to <2,000 calories (8,360 kJ) per day	1	2	0	0	1	1	101,714	6,891	94,823	93	73
6. Reduce dietary fat to <25% of calories as fat	2	6	0	0	1	5	127,942	18,476	109,466	86	46
7. Moderate intakes of lean red meat can be eaten as part of a mixed diet including carbohydrates (breads and cereals), vegetables and fruit, and dairy products; charring of red meat is best avoided; consumption of processed meats should be limited	3	3	0	0	1	2	567,185	142,252	424,933	75	70
8. Eat five or more servings per day of a variety of vegetables; national nutrition guidelines also advise two servings of fruit daily ("Go for 2 and 5")	1	6	0	0	1	5	541,481	144,204	397,277	73	45
9. Select poorly soluble cereal fibers (e.g., wheat bran), especially if at increased risk for colorectal cancer	3	4	0	0	0	4	38,223	19,896	18,327	48	44
10. Ensure a total calcium intake of 1,000–1,200 mg/day in keeping with general dietary guidelines	1	4	0	0	0	4	545,684	208,729	336,955	62	59
11. Selenium supplementation for chemoprevention is promising but requires confirmation	1	3	0	0	0	3	1,927	1,476	451	23	25
12. Antioxidant vitamin supplementation is not advised at present to protect against colorectal cancer	1	4	0	0	0	4	1,389	999	390	28	34
13. Aspirin should be considered as prophylaxis against further adenoma development in those with previous removal of an adenoma	3	7	1 (272)	1	1	4	81,816	38,959	42,857	52	47
14. HRT cannot be recommended as prophylaxis against colorectal cancer because of its possible collateral risks, including breast cancer	1	4	0	0	3	1	96,138	2,111	94,027	98	100

[a]Number of female participants divided by total number of participants, included in all studies where the sex of participants was recorded.
[b]Median was calculated by listing the percentages of female participants in each of the studies where the sex of participants was recorded and identifying the middle number.
BMI, body mass index; HRT, hormone replacement therapy.

Table 4. Number and Percentage of Male and Female Participants per Recommendation in Diabetes Guidelines

Recommendation	References Excluded	References included	Sex not recorded	Sex recorded							
			Studies (no. of participants)	Male only	Female only	Male and female	No. of participants	No. of male participants	No. of female participants	% female participants[a]	Median % female[b]
1. Since obesity is associated with an increased risk of type 2 diabetes, interventions to reduce obesity may reduce the risk of type 2 diabetes	0	24	4 (4,755)	8	2	14	269,802	93,540	176,262	65	48
2. Abdominal obesity is an important indicator of increased risk of type 2 diabetes in all ethnic groups and should be a particular focus of weight loss programs	0	22	1 (721)	6	5	11	132,414	70,597	61,817	47	56
3. Waist circumfrence should be used in addition to BMI to identify individuals who should seek and be offered weight management programs	0	11	0	2	2	7	122,762	64,723	58,039	47	51
4. Regular physical activity is recommended to reduce the risk of type 2 diabtetes	0	15	0	8	1	6	160,719	68,089	92,630	58	0
5. Physical activity should be measured in free-living subjects by movement recorders, particularly the pedometer, questionnaires focusing on leisure time activities, heart rate monitoring; functional aerobic capacity should be measured from predictive equations based on gender, age, self-reported physical activity, and body composition or BMI	0	16	2 (36)	3	3	10	4,699	3,900	799	17	38
6. Individuals at risk of developing type 2 diabetes should have dietary intake assessed and should receive individualized dietary advice and continued dietetic support; individuals at risk should consume a diet with <30% energy as fat, with <10% as saturated fat	0	14	1 (666)	2	3	9	94,329	4,197	90,132	96	58
7. Identification of women with GDM would allow postnatal clinical interventions in those with diabetes persisting after delivery, the option to use preventive methods to reduce the risk of type 2 diabetes	0	16	0	0	14	2	60,735	605	60,130	99	100
8. In view of the association between low birth weight and later development of diabetes, studies are required to evaluate	1	15	0	5	5	5	98,713	26,547	72,166	73	49

(*continued*)

Table 4. (Continued)

Recommendation	References Excluded	References included	Sex not recorded	Sex recorded							
			Studies (no. of participants)	Male only	Female only	Male and female	No. of participants	No. of male participants	No. of female participants	% female participants[a]	Median % female[b]
interventions aimed at reducing low birth weight and the impact this has on the development of type 2 diabetes											
9. Diets of low energy density and containing a wide range of carbohydrate foods rich in dietary fiber and of low glycemic index (cereals, vegetables, legumes and fruits) are recommended to reduce the risk of type 2 diabetes	0	2	0	1	1	0	107,932	42,759	65,173	60	50
10. More research is required to assess the impact of psychologic stress or a major depressive episode in affecting the risk of type 2 diabetes	0	9	1 (25,019)	1	0	8	20,038	12,610	7,428	37	50
11. Programs of diet and exercise education in children should include parental involvement and use behavioral techniques to reinforce lifestyle change	3	22	2 (81)	2	6	14	16,908	11,197	5,711	34	71

[a]Number of female participants divided by total number of participants included in all studies where the sex of participants was recorded.
[b]Median was calculated by listing the percentages of female participants in each of the studies where the sex of participants was recorded and identifying the middle number.
GDM, gestational diabetes mellitus.

Colorectal cancer

From the NHMRC colorectal cancer guidelines,[18] we excluded 27 references. Fifty-eight articles, published between 1987 and 2005, were included in our analysis (Table 3). Two of these articles, including 490,251 participants, did not record the research subjects' sex. The remaining 56 articles included a total of 4.1 million participants. Overall, 67% of the participants were female; the mean percentage of females was 54% and the median was 46%. Only 5% of studies were male-only, whereas 21% of studies included female-only populations. The substantial difference between the median (46%) and overall (67%) percentage of females is due to the large number of female-only studies.

In relation to specific recommendations, Recommendation 1 addresses physical activity; the research underpinning this recommendation is based on studies with 93% males (median percentage of females across the three studies was 44%). In contrast, Recommendations 2, 5, and 6, which deal with weight and calorie control, are based on studies that have 59%, 93%, and 85% females (with respective medians of 78%, 73%, and 46% females).

Depression

The BeyondBlue depression guidelines[20] were based on 106 references, of which 105, published between 1984 and 2001, are included in our analysis. Eight studies did not record the sex of participants; this represented 9.9% of the overall participants. The remaining 97 studies included a total of 15,875 participants, and all studies included both males and females. Overall, 64% of the participants were female; the mean percentage of females was 64% and the median was 66%.

Type 2 diabetes

From the NHMRC diabetes guidelines,[19] we excluded 4 references and based our analysis on the remaining 166 articles published between 1973 and 2002 (Table 4). Eleven articles, including 31,197 participants, did not record the participants' sex. The remaining 155 studies included 1.1 million participants. Overall, 63% of the participants were female; the mean percentage of females was 53% and the median was 50%. Interestingly, the diabetes studies included a much higher proportion of sex-specific studies than did the other guidelines; 23% of studies were male-only, and 25% were female-only.

As with the colorectal cancer guidelines,[18] there were specific recommendations in the diabetes guidelines about exercise.[19] Recommendation 1 relates to physical activity and is broken down further into eight specific recommendations. Of these, four apply to both men and women; three of these are based on research with both men and women, whereas one is based on evidence derived from males only. The remaining four exercise-related recommendations are for men only, based on research with males.

Appropriate representation of women in the selected evidence base

The final part of the analysis compared the rates of participation of women in the guidelines reviewed here with the proportions of women affected by the condition.

Antiarrhythmics

Women represented 35% of the overall research participants (median 38% across the 44 studies). The clinical picture of AF is complex, so we explain here the age-related incidence of AF in order to contextualize the results. The median age of patients with AF is 75 years,[23] and the diagnosed rate of AF is 5% in women and 7.3% in men at 75–79 years. The actual population rate (both diagnosed and undiagnosed) has been measured in patients 85+ and is 12.1% in women and 16.6% in men.[24] Because of women's increased life span, they account for 60% of patients aged 75+ with AF in the United States.[25] The risk of stroke and mortality associated with AF is significantly higher in women.[25] There is an important interaction among age, stroke risk, and sex, with female AF patients >age 75 at particularly high risk for stroke.[23] Prevalent AF has been associated with a 50% excess in all-cause mortality in men compared to a 90% excess in women.[26] The proportion of women in AF research in this review does not reflect the population incidence or the impact of AF on women's health.

Chronic fatigue syndrome

Clinical studies can show a ratio of up to 1:4 male/female CFS patients.[27] However, population studies indicate that the rate of CFS among males is higher and suggest a ratio of 1:2.[28] It is possible that women are more likely than men to seek clinical treatment for CFS. Of the participants in the studies we analyzed, 70% were female, which reflects the estimated population ratio of 1:2.

Colorectal cancer

Australian Institute for Health and Welfare (AIHW) data show that Australian women suffer from 46% of the annual 63,605 disability adjusted life years (DALYs) lost to colon and rectal cancer and also 46% of the annual 4,871 deaths.[21] Measured against this baseline, women were overrepresented in the evidence supporting the NHMRC colorectal guidelines,[18] representing 67% of the overall research participants. However, the mean was influenced by a large number of female-only studies. The median percent female participants across the studies was 46%, which more accurately reflects the sex distribution in the patient population.

Depression

Women are more affected by unipolar depression (UPD) than men, accounting for two thirds of the global annual 65 million DALYs and half the suicide rate associated with UPD in 2004.[22] The greater proportion of female participants in the BeyondBlue depression-related studies[20] (66% female) accurately reflects the population affected by this condition.

Type 2 diabetes

In Australia, women account for 46% of the 132,940 DALYs lost to type 2 diabetes and also 46% of the 3,130 deaths resulting from type 2 diabetes each year.[21] Women, at 63% of the research participants, were therefore overrepresented in the diabetes research studies referenced by the NHMRC diabetes guidelines.[19]

Discussion

To our knowledge, this is the first study to review the inclusion of women in research used to develop an international selection of clinical practice guidelines. Two prior studies conducted in the Netherlands focused on sex-related factors in the development of Dutch clinical guidelines.[29,30] These showed that the authors of the guidelines did not pay special attention to sex-related differences when developing the guidelines[29] and that the number of sex-specific recommendations ranged from 0 of 148 recommendations in depression guidelines to 16 of 84 recommendations in osteoporosis guidelines.[30] Keuken et al.[29] concluded that the lack of sex-related evidence in the published literature is a major contributory factor to the lack of sex-specific recommendations in guideline documents. Melloni et al.[31] used the 2007 American Heart Association guidelines to identify randomized controlled trials (RCTs) in their investigation of female participation rates in RCTs of CVD prevention; they found underrepresentation of women in these trials.

Cardiovascular research

Exclusion of women from cardiovascular research has been one of the widely discussed examples of the underrepresentation of women in clinical research and is thought to contribute to the undertreatment of CVD in women.[32] We, therefore, expected higher rates of female participation in the evidence base for this review addressing the use of antiarrhythmics.

The US National Institutes of Health (NIH) Revitalization Act[6] came into force in 1993, requiring appropriate inclusion of women in publicly funded clinical research. Twenty-eight of the 38 antiarrhythmics articles (74%) were published after 1993; however, many of the studies would already have enrolled participants before the regulatory change. However, 20 of 38 (53%) articles were published in or after 2000, by which time one would expect the inclusion rates of women to be increasing both as a direct response to the NIH requirements and indirectly as part of the increased recognition of the need to include women in cardiovascular research. The percentage of women in these studies is no greater than in the full dataset. In the 20 studies published after 2000, the range of percentage of women is 1%–51%, the median percentage of women was 36%, and only 33% of the 8,188 participants in these studies were female. This result suggests persistent bias against the inclusion of women in cardiovascular research.

The study including only 1% female participation was conducted by the SAFE-T 2000 research group[33] and involved 665 patients recruited from Veterans Affairs organizations in the United States. The recruitment strategy clearly explains the overwhelming proportion of male participants, but the authors do not address this as a limitation of the study, restrict their conclusions to male patients, or discuss the potential role of sex as a variable in the effectiveness of amiodarone vs. sotalol for atrial fibrillation. Yet a study has shown the risk of bradyarrhythmia requiring pacemaker insertion associated with amiodarone use for AF is significantly greater in women than in men, independent of weight or body mass index.[34]

Given the clinical picture of AF, it is disturbing that AF-related evidence-based guidelines are based on research conducted primarily with males. Our findings support previous reviews showing that contemporary guidelines for prevention, diagnostic testing and medical and surgical treatments for CVD are still based on studies conducted predominantly with men.[31,35]

Gender stereotypes relating to diet and exercise

Recommendations within the colorectal cancer and diabetes guidelines reflected gender stereotyping. Women formed the majority of participants in research for diet-related recommendations, and this was not noted in the guideline. In relation to exercise, the diabetes guideline developers noted the sex of research participants in the majority of cases, leading to a predominance of male-only recommendations that accurately, if uncritically, reflects the comparative lack of research into the effects of exercise in women.

The small sample sizes considered here provide insufficient data to show systematic stereotyping. However, the data correlate with previous findings showing gender stereotyping in sex-specific injury prevention studies, where studies with men recruited athletes and focused on peak performance, whereas studies with women focused on prevention of falls among the elderly.[36]

Analysis of sex differences

The conditions we considered all have recognized sex differences, yet sex and gender were rarely discussed in the body of the guidelines. In the two reports where women were overrepresented or underrepresented in the research population, there was no acknowledgment of this as a limitation of the research base or on the applicability of the guidelines to the wider population. Sex and gender factors were not discussed in the antiarrhythmic guidelines.[16] The underrepresentation of women in the research base is not mentioned in the section addressing risk of bias in included studies. Subgroup analysis by sex was not conducted.

The CFS guidelines[17] discussed sex differences, stating that CFS affects women at approximately four times the rate of men. This refers to the clinical ratio (1:4) rather than the estimated population ratio (1:2). Relative to the clinical ratio, women are underrepresented in the research base supporting these guidelines (70% female), but this is not mentioned by the reviewers. There are no other substantive references to sex or gender. (The only additional sex-related comments were in relation to 2 studies that were excluded from the analysis. It is unclear whether the studies were partially excluded because they were female-only populations or the sex of the research participants was incidental.)

The colorectal cancer guidelines[18] include 13 recommendations in Chapter 2 regarding primary prevention of colorectal cancer; 3 of these include sex-specific comments. The literature base supporting each recommendation is discussed, and the varying applicability of results to men and women is mentioned in relation to physical exercise, obesity, and alcohol consumption. Recommendation 3 provides sex-specific guidelines for limiting energy intake in men and women, but the discussion does not mention that 93% of the overall research population referenced was women. Selenium and antioxidant vitamin supplementation (recommendations 11 and 12) were based on research with approximately 75% males, but this was not noted by the reviewers.

There is no discussion about the impact of sex or gender in the BeyondBlue depression guidelines.[20] The recommendations

are organized according to the type of depression (mild, moderate, or severe) and the presence of other relevant comorbidities.

The NHMRC type 2 diabetes guidelines[19] state that the recommendations should be used only as a guide and applied to individual patients with caution to assist clinical decision making. The individual recommendations in this guideline use various qualifiers including people, men and women, men only, and women only, or have no qualifier. In some cases, for example, in relation to the evidence statement that: "In both men and women, physical activity reduces the risk of type 2 diabetes," there is acknowledgment that women have been less well studied on this topic. In other cases, for example, the evidence statement: "Weight loss is associated with reduced progression of IGT [impaired glucose tolerance] to Type 2 diabetes," most of the data are from research with women, but there is no sex qualifier on the advice. The role of sex is not discussed in any detail, apart from a discrete section in the guidelines that deals with gestational diabetes.

Limitations of our study

Our study has several limitations. First, because of the time-consuming methodology, we were able to analyze only a small number of the many evidence-based guidelines available. Second, our methodology had to be adapted to the specific review processes of each guideline, which limits the comparability of the results across the guidelines. For example, the NHMRC guidelines are organized into specific recommendation. A single study could be used to support multiple recommendations and was, therefore, counted multiple times in our analysis. In contrast, the Cochrane review indicated when multiple articles referred to the same study and identified the major study; in our analysis, we included only the major study and can be confident that research populations were not counted more than once. Third, we have not systematically coded the text of the guidelines or cross-referenced the text to the supporting research to determine if all clinical recommendations are appropriately supported by research with both sexes. However, we did conduct an analysis of the NHMRC colorectal cancer and diabetes guidelines because these documents were organized according to specific recommendations.

Conclusions

Clinical guidelines do not always or consistently take account of the sex of participants in research. Whereas three of the guidelines that we studied were based on research populations that accurately reflected the sex distribution of the condition in the general population, women were overrepresented in the diabetes guidelines and significantly underrepresented in the antiarrhythmic guidelines. In addition, there was varying attention to sex differences, with examples of recommendations for both sexes based on research with one sex, often without clarification or qualification. Sex-specific recommendations relating to exercise uncritically reproduced gender stereotyping.

We support the recent Institute of Medicine recommendation that journals require reporting data on men and women separately and provide sex-specific analyses for all publications.[37] This will oblige researchers to design studies that can provide separate and independent answers for men and women. Guideline developers are dependant on the research evidence available, but they are also responsible for how they frame their questions and analyze the evidence. Guideline developers should ask separate questions about the health of men and women and explicitly look for evidence to answer these questions. In the absence of sex-specific evidence, recommendations should be suitably qualified in order to inform practice and guide future research.

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