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Attention to Sex-Related Factors in the Development of Clinical Practice Guidelines

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ABSTRACT

Background: **Clinical practice guidelines describe optimal strategies for disease prevention, diagnosis, or treatment. Increasing evidence indicates that sex-related factors may have an impact on these strategies. We examined the way in which two Dutch guideline organizations address evidence on sex factors in their guideline development methodologies. We then determined whether attention to these factors could be improved and, if so, how this could be done.**

Methods: **We selected seven recent guidelines on four conditions: hypertension, depression, osteoporosis, and rheumatoid arthritis. We studied information obtained from interviews with members of the guideline committees and analyzed the content of the guideline documents themselves. Our findings were discussed at an expert meeting.**

Results: **We found that all the guideline committees concerned applied an internationally accepted framework for guideline development. The proportion of male members ranged from 67% to 100%. None of the guidelines included a question (or subquestion) focusing on sex-related factors. In the literature searches no sex-specific search terms were used. Critical appraisals did not include any systematic focus on sex-related factors or effects. The number of sex-specific recommendations (relative to the total number of recommendations) ranged from 0 of 82 and 0 of 148 in the guidelines on depression to 16 of 84 in one of the guidelines on osteoporosis.**

Conclusions: **We found that when developing guidelines, none of the committees systematically focused on sex-related factors that might be relevant to the way in which evidence is identified, appraised, or described. A number of recommendations were made with the aim to facilitate greater attention to sex-related factors in the current methods of guideline development.**

INTRODUCTION

TRADITIONALLY, CLINICAL RESEARCH on conditions that affect both men and women has largely been restricted to male populations,[1] and in the 1990s, various public and scientific concerns were raised about this approach. It was feared that the results of such research might not be applicable to the clinical population as a whole, thereby preventing women from receiv-

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ing the best possible care.[1] In response to these concerns, researchers and organizations funding health research have taken measures to ensure the equitable inclusion of men and women in relevant clinical research and analysis of the data according to sex.[1–6] This approach has produced new evidence indicating that for many diseases, the diagnostic and treatment strategies developed on the basis of research in men may not be appropriate for women.[7] In the case of acute coronary syndromes, for example, the incidence of atypical symptoms is higher in women than in men.[8] This has implications for the optimal diagnostic strategy in such cases. Another example concerns antidepressants. Here, as a result of different pharmacokinetic characteristics, women may need lower dosages than men.[9]

In current clinical practice, clinical guidelines have a growing impact on decision making in the area of health care,[10] providing systematically developed, evidence-based recommendations concerning the optimal strategies for diagnosis and treatment in specific clinical circumstances.[11] Guidelines are generally produced by an interdisciplinary group of experts under the auspices of a relevant professional organization.[10] The process of guideline development, which is becoming increasingly formalized,[12] currently includes the following stages: the formulation of clear key questions, a systematic review (involving a verifiable systematic search of existing evidence and a critical appraisal of the evidence in question), and the phrasing of useful recommendations for clinical practice.[13]

If the quality of care for both women and men is to be improved, it is crucial that new evidence on sex-related factors be taken into consideration when developing clinical guidelines. However, none of the resources available to guideline developers (such as handbooks or user guides) provide comprehensive instructions on how they should incorporate a focus on sex-related factors into guideline development. For example, the World Health Organization's (WHO) handbook for guideline developers recommends that there should be a gender balance in the composition of WHO guideline committees[14] to give both sexes an equal voice. With regard to the review of clinical evidence and the formulation of recommendations, other handbooks suggest that issues relating to sex, ethnicity, and individuals with special needs should also be considered.[15] However, these publications provide no details how this should be done. AGREE (an instrument for appraising the quality of clinical guidelines that was developed at an international level) includes the quality criterion that the patients to whom a guideline is meant to apply should be described specifically.[16] However, only in the user guide of the instrument, and not in the main text, it is explained that sex, age range, and the severity of the condition of the target population may be provided in this description.[16]

A number of sex-specific clinical guidelines have recently become available.[17–19] These guidelines focus on new clinical evidence relating to women; in addition, the guideline committees involved included experts in gender medicine. Most guidelines pertain to both men and women, however, and the majority of guideline developers are not familiar with the field of gender medicine.

We, therefore, conducted a study to determine if current guideline development procedures incorporate any barriers to the systematic consideration of sex-related factors. To this end, we examined the extent to which sex-related factors were considered during the development of clinical guidelines produced under the auspices of two prominent Dutch guideline organizations. Both organizations, the Dutch College of General Practitioners (NHG) and the Dutch Institute for Healthcare Improvement (CBO), have extensive experience of guideline development. Both have adopted the internationally accepted procedures for guideline development, and they also work in accordance with the principles of evidence-based medicine when locating and reviewing research evidence.[10]

In gender medicine, it is common to make a distinction between the concepts of "sex" and "gender." The term "sex" refers to the biological and physiological characteristics that define men and women. "Gender" refers to the socially constructed roles, behaviors, activities, and attributes that society considers appropriate for men and women.[20] Because of the nature of clinical guidelines, patients' socially constructed roles, behaviors, activities, and attributes typically receive less consideration than their biological and physiological characteristics. Accordingly, our study has focused solely on the consideration given to sex-related factors in guideline development. Our exploration of the guidelines centered around the following questions:

1. What is the balance between the numbers of men and women in guideline committees?

2. Do guideline committees include experts in gender medicine?
3. To what extent do the individual steps of guideline development (the formulation of key questions, the formulation of a search strategy for locating relevant literature, and the appraisal of the selected literature) involve the consideration of potentially relevant sex-related factors?
4. To what extent is sex-specific evidence presented in the guidelines?

MATERIALS AND METHODS

We analyzed a number of NHG and CBO guidelines that were developed between 1999 and 2002. The two organizations often develop guidelines on similar topics. NHG develops guidelines for general practitioners, and CBO develops guidelines for medical specialists and those involved in multidisciplinary care. We restricted our study to guidelines dealing with medical conditions that involve potentially relevant differences between men and women, for which some evidence is available in the literature.

Of the seven guidelines selected, two dealt with hypertension, two with depression, two with osteoporosis, and one with rheumatoid arthritis (RA) (Table 1). By means of literature searches in PubMed and EMBASE, we were able to locate potentially relevant sex-specific data for each of these conditions. Some examples of these data are shown in Table 2, and further details are in the possession of D.G.K.

The following three methods were used to answer the research questions:

1. To find answers to the first three questions, semistructured interviews were held with members of the guideline committees. One to three members were selected for interview on the basis of their availability and their assumed knowledge of the guideline development process (Table 1). In the case of two of the NHG guidelines (Table 1, HYP1 and RA), the clinical librarian/information specialist responsible for the search strategy used was also interviewed. D.G.K. conducted and transcribed the interviews and checked the information given by the interviewees against the latest available guidelines (or other documents produced by the guideline committees).

2. To answer the fourth question, a content analysis of sex-specific statements was conducted on the most recent documents pertaining to the selected guidelines. This analysis focused specifically on three subsections of the guidelines: epidemiology, underlying evidence, and recommendations. Details of the content analysis are available from D.G.K.

3. An expert meeting involving 22 participants was held to validate our findings and to discuss the implications. The participants were selected on the basis of their experience in guideline development, health research, or gender medicine. The group of experts included the directors of the guideline departments of the NHG and CBO (2), a staff member of CBO (1), guideline committee members (2), health researchers (3), clinicians (2), health research policymakers (3), professors in health care (2), researchers in gender medicine (5), an international expert in guideline development (1), and one international advisor in the field of gender medicine (1). The participants were asked if they recognized the findings (and, if so, to what extent) and if they could explain them. They were also invited to suggest ways in which possible barriers to the consideration of sex-related factors in guideline development might be removed.

RESULTS

Table 3 provides specific information on the first three research questions.

Composition of guideline committees

Guideline committees typically consist of a chair, a staff member from the relevant guideline organization, and several other members. These individuals are usually nominated by their respective professional organizations on the basis of their expertise in the field covered by the guidelines in question. CBO committees are usually larger than NHG committees.

Four of the guideline committees responsible for the seven guidelines that we studied had a male chair, one had both a male and a female chair, and two had no chair at all. Five committees were supported by a male staff member from the guideline organization itself (Table 3). The proportion of male members ranged from 64% for the NHG guideline on osteoporosis (OST1) to 100% for the CBO guideline on hypertension

Table 1. Details of Seven Selected Guidelines and of Individuals Interviewed

Title	*Abbreviation*	*Organization responsible for development*	*Year of publication*	*Focus*	*Reason for development/revision*	*Individuals interviewed*
NHG[a] Practical Guideline on Hypertension (revision)	HYP1	NHG[a]	Draft version in 2002	Case identification, diagnosis, therapy	New evidence on pharmacotherapy	Advising staff member, committee member, information specialist
Revised Guideline on Hypertension (revision)	HYP2	CBO[a]	2000	Case identification, diagnosis, therapy	New thinking on cardiovascular disease risk management	Advising staff member, two committee members
NHG Practical Guideline on Depressive Disorders (Depression) (revision)	DEP1	NHG	Draft version in 2002	Case identification, diagnosis, therapy	New severity classification system; new insights into treatment options for GPs	Committee member
Multidisciplinary Guideline on Depression: diagnosis and treatment of adult clients with a depressive disorder (revision)	DEP2	CBO	Draft version in 2002	Case identification, diagnosis, therapy	Division of tasks between different healthcare providers	Advising staff member, chair, former committee member
NHG Practical Guideline on Osteoporosis (new)	OST1	NHG	1999	Prevention, diagnosis, therapy	Inconsistencies between national guidelines on this topic	Committee member
Osteoporosis: second, revised, guideline (revision)	OST2	CBO	2002	Prevention, diagnosis, therapy	Differences between NHG and CBO guidelines on this topic	Advising staff member
Rheumatoid Arthritis (revision)	RA	NHG	Draft version in 2002	Case identification, diagnosis, primary therapy	New treatments and the importance of early referral to specialist	Advising staff member, information specialist

[a]NHG, Dutch College of General Practitioners; CBO, Dutch Institute for Healthcare Improvement.

Table 2. Examples of Available Evidence That Potentially Implicates Sex-Related Factors in Hypertension, Rheumatoid Arthritis, Depression, and Osteoporosis[a]

Hypertension
The antihypertensive drug verapamil is a controlled-onset, extended-release calcium antagonist. It induces a 24-hour reduction in systolic and diastolic blood pressure that is more pronounced in women than in men (systolic blood pressure −15.1 vs. −10.0 mm Hg, $p < 0.001$; diastolic blood pressure −10.4 vs. −8.2 mm Hg, $p < 0.003$).[21]
Treatment with diuretics is associated with a risk of developing renal cell carcinoma. The risk to women is more than twice as great as that to men. This is shown by the ODDs ratio for renal cell carcinoma, which compares the risk to users of diuretics with the risk to nonusers. In women, this ratio has a value of 2.01 (95% CI 1.56 to 2.67); in men, it is 1.69 (95% CI 1.34 to 2.13).[22]
As they receive less optimal antihypertensive treatment than men of the same age, menopausal women with hypertension have a poorer prognosis. Accordingly, there should be special consideration for antihypertensive drug treatment in menopausal women.[23]
Rheumatoid arthritis (RA)
Erosive disease resulting from RA tends to occur more frequently in men than in women (72% vs. 55% $p < 0.05$). In addition, men develop this condition at an earlier stage in the disease process (47% within the first 4 years of RA, as opposed to 31% of female patients).[24]
GPs take longer to refer female patients with symptoms of RA to specialized care than they do male patients with the same level of disease activity (median of 93 days vs. 58 days, $p = 0.008$).[25]
RA appears to be influenced by sex hormones: there is a remission of the disease during pregnancy, RA flares in synchronization with the menstrual cycle have been reported, and there is some evidence that oral contraceptives are protective.[26]
Depression
For pregnant women with depression, suspending antidepressant therapy during pregnancy may cause significant morbidity for the patient. The potential risk to the fetus from the drug exposure needs to be outweighed by the risk of untreated maternal depression.[27]
The incidence of comorbid anxiety disorder among patients with depression is three times greater in women than in men.[28]
Osteoporosis
Osteoporotic fractures in men are associated with higher mortality and morbidity than in women.[29]

[a]Literature available at the time the selected guidelines were being developed (between 1999 and 2002) and information not present in the guidelines that were selected for this study.

Table 3. Attention to Sex-Related Factors in Successive Stages of Guideline Development for Seven Selected Guidelines

Guideline document	*HYP1*	*HYP2*	*DEP1*	*DEP2*	*OST1*	*OST2*	*RA*
Composition of committee							
Sex of chair	Male	Male	No chair	Male	Male and female	Male	No chair
Sex expertise present	No	No	No	No	Yes	No	No
Sex of staff member[a]	Male	Female	Male	Male	Male	Female	Male
Number of female members relative to total number of members (%)	0/6 (0%)	2/15 (15%)	2/7 (29%)	9/26 (35%)	4/11 (36%)	3/21 (14%)	0/6 (0%)
Attention to sex factors in key questions[b]	No	No	No	No	No	No	No
Attention to sex factors in search strategies[c]	No	No	No	No	Unclear	Unclear	No
Specific attention to sex factors in critical appraisal[d]	Yes	No	No	No	No	Yes	No

[a]That is, the NHG or CBO staff member on the guideline development committee.

[b]Attention to sex-related factors in key questions is defined as a key question in which a reference is made to men, women, or both.

[c]Attention to sex-related factors in the search strategy is defined as a search with specific search terms that are intended to identify literature on sex-related health topics, e.g., for PubMed "sex ratio [MeSH]," "sex distribution [MeSH]," "sex factors [MeSH]," "sex characteristics [MeSH]," "sex differentiation [MeSH]," "gender differences [tw]," "sex differences [tw]," "gender [tw]."

[d]Attention to sex-related factors in the critical appraisal phase is defined as a critical appraisal in which the patient's sex is considered in outcomes or one involving specific subgroups of men and women or one focusing on differences between the sexes in terms of outcome.

(HYP2) and the NHG guideline on RA (Table 3). The committee responsible for the NHG guideline on osteoporosis was the only one to include a member with specific expertise on sex-related factors in health.

The process of guideline development

Our study revealed that none of the committees had used a specific key question (or subquestion) on sex-related factors affecting the target condition as a starting point for guideline development. The 1994 version of the CBO guideline on depression did contain one sex-specific key question, but this was omitted from the revised edition of this guideline published in 2002.

In all cases, the literature searches carried out during guideline development were restricted to drug treatment (HYP1, HYP2, RA) or various other special topics (DEP1, DEP2, OST1, OST2) (Table 1). In two cases (OST1, OST2), the actual bibliographic search strategies used could not be retraced. However, those search strategies that were still available showed that none of the specific search terms used would have facilitated the retrieval of sex-specific information.

Finally, we found no evidence of a systematic focus on potentially relevant sex-related factors either in the review or in the critical appraisal of the literature. However, the text of the CBO guideline on osteoporosis (OST2) acknowledges that most of the available evidence about this condition was drawn from studies in women and that these findings had been extrapolated to men in the absence of evidence from research in male patients. A footnote to the NHG guideline on hypertension (HYP1) mentions that most of the research on hypertension has been carried out in men. Similar statements could not be found in the other guidelines.

The content of the guidelines

Guidelines typically consist of a number of different sections, including epidemiology, underlying evidence, and recommendations. All the guidelines provided some sex-specific data in their epidemiology sections (Table 4). For example, the RA guideline stated: "Up to the age of 45, the male:female ratio (for the prevalence of rheumatoid arthritis) is 1:3, among older people ratio differences between the sexes are small." (Table 1, RA.) When presenting supporting evidence, all the guidelines made at least one reference to sex-related factors. For example, the OST2 guideline stated: "Osteoporosis occurs most often in women. Osteoporosis in men and children is not well documented. There has been little research in this area. Most published research concerns women, particularly white women. Little to no research has been carried out on non-white women." (Table 1, OST 2.)

The two guidelines on osteoporosis both made more references to evidence on sex-related factors than the other guidelines. One of them (OST2) also contained the highest number of sex-specific recommendations relative to the total number of recommendations (16 of 84). In the other guidelines, the corresponding figures ranged from 0 of 82 and 0 of 148 (DEP1, DEP2) to 4 of 90 (HYP1). An example of a sex-specific recommendation from the OST2 guideline is: "Women with an osteoporotic fracture of the spine or the hip under the age of 50 or men with an osteoporotic fracture of the spine or the hip under the age of 65 must be referred to a specialized care provider for further evaluation of the underlying cause." (Table 1, OST 2.)

Expert meeting

Our findings were discussed during an expert meeting that took place on May 13, 2003. The participants acknowledged that women were underrepresented on the guideline committees. They saw this as an example of a more general trend, as women are still underrepresented on governing bodies in the field of medicine. They also acknowledged that the methodology of guideline development generally fails to take sex-related factors into account. Several explanations were put forward to account for these observations. This situation could be due to the general lack of awareness among guideline developers concerning the importance of considering sex-related factors when drawing up clinical guidelines. There is also a general lack of know-how among guideline developers concerning the questions and methods for determining how sex-related factors might affect an individual's condition. Another contributory factor might be a lack of relevant evidence on sex-related factors specific to the topic of the guideline in question. It was agreed that improvements were needed, and several recommendations were put forward to this end.

Table 4. Attention to Sex-Related Factors in Various Subsections of Seven Selected Guidelines

	Guideline	*HYP1*	*HYP2*	*DEP1*	*DEP2*	*OST1*	*OST2*	*RA*
Number of statements in text referring to sex factors	Subsections							
	Epidemiology[a]	3	1	1	1	9	17	4
	Underlying evidence[b]	5	9	6	9	34	134	2
	Recommendations[c]	4	2	0	0	2	16	2
	Total recommendations[c] in text	90	224	82	148	52	84	70
	Number of recommendations referring to sex factors relative to total number of recommendations	4/90	2/224	0/82	0/148	2/52	16/84	2/70

[a]Epidemiological statement: This is a statement that contains data on occurrence rates for the topic of the guideline. An epidemiological statement referring to sex-related factors is a statement that refers to men, women, or both.

[b]Underlying evidence: This is defined as any statement that provides evidence (or proof) to support a recommendation. Underlying evidence referring to sex-related factors is defined as a statement that contains a reference to men, women, or both.

[c]Recommendation: A recommendation is defined as: "[A] systematically developed statement[s] to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances." [14]We identified such recommendations by using a list of words and expressions urging physicians to act in a particular way (more details available from D.G.K.). A recommendation referring to sex-related factors is one that refers to men, women, or both.

DISCUSSION

Overall, the results show that none of the guideline committees have given systematic attention to potentially relevant evidence on sex-related factors. This is reflected both in the process of guideline development and in the content of the guidelines themselves. In terms of composition, the majority of guideline committee members were men, and only one committee (OST1) included an expert in gender medicine. The most striking aspect of these findings is that some evidence implicating the relevance of sex-related factors for all the target conditions was available when the guidelines were developed (Table 2).

Our study, which was exploratory in nature, was restricted to the practices of seven Dutch guideline committees. However, the implications of our data were acknowledged by a wider group of experts selected on the basis of their knowledge of guideline development practices and of gender medicine. We are confident that this procedure gives a reasonably accurate impression of the way in which Dutch guideline committees deal with sex-related factors.

To be fair, it should be acknowledged that some changes have taken place since 2002. In 2004, CBO and NHG published a common handbook for guideline developers that includes a chapter on diversity issues in guideline development.[30] Since 2004, both organizations have been participating in an intervention study aimed at giving increased consideration to sex-related factors during guideline development.

Despite the growing numbers of women in the medical profession, we observed that they were underrepresented on the guideline development committees. At the expert meeting, it was suggested that women might still encounter personal and structural barriers to participation at higher levels of biomedical research and health policy development. A similar trend was observed by the U.S. Office of Research on Women's Health, which put forward some recommendations with a view to removing any such barriers.[31]

We observed that guideline committees paid little attention to sex-related factors. They typically seemed to aim for general recommendations applicable to all patients. During the expert meeting, it was suggested that the scant consideration given to sex-related factors reflects a more general neglect of potentially relevant patient characteristics (e.g., ethnicity, age, socioeconomic circumstances) in guideline development. There is a lack of awareness that neglecting such characteristics may adversely affect the quality of a guideline's recommendations. This can be an important barrier to the consideration of sex-related factors in guideline development.

Taking sex-related factors in consideration in guideline development requires more than awareness alone; individuals must also be competent in the use of methods for achieving this aim. In the first place, one needs to be able to ask the proper questions.[7,32] Second, it is also important to know which search terms can be useful for locating sex-specific research,[30] to understand how the effects of sex-related factors should be considered in the analysis (or meta-analysis) of research evidence,[33] and to be able to evaluate the value of such research for clinical practice. Our study has shown that guideline developers lack a comprehensive set of directions on such issues. This, in turn, may represent a barrier to the consideration of sex-related factors in guideline development.

We found that only one of the guideline committees included an expert in gender medicine (OST1). The final document of the resultant guideline contained a relatively large number of statements referring to sex-related factors. This suggests that, when considering the role of sex-related factors, the involvement of such experts in guideline development may be a useful asset. In the Netherlands, however, individuals with expertise in gender medicine are still relatively few in number. Dutch medical schools have recently started to offer integrated courses on sex-related factors and health care.[34] Courses of this kind may help to raise awareness of sex-related aspects of health among future guideline developers. There are ongoing efforts to promote the consideration of sex-related factors in clinical research and in the presentation of research findings.[33,35] In the future, this will certainly facilitate a greater awareness of sex-related factors in guideline development.

One limitation of this study is that it was restricted to just two highly experienced guideline organizations in a single country, the Netherlands. We should, therefore, be cautious about extrapolating the results to all such organizations, whether at home or abroad. In contrast to the handbooks for guideline developers issued by the two Dutch guideline organizations dealt with here (NHG and CBO), some other organizations'

handbooks encourage a gender balance on guideline committees.[14] These publications also state that, where relevant, there should be a focus on specific topics, such as sex-related factors, in systematic literature reviews and in the formulation of recommendations.[13,15,16] In general, however, there are no significant differences between the framework for guideline development used by these Dutch organizations and international standards in this field. Moreover, other organizations' handbooks also contain relatively little information on the consideration of sex-related issues. For those reasons, we believe that our results are also relevant to other organizations. There is a growing recognition, both in the Netherlands and elsewhere, that clinical guidelines should address diversity in the patient population.[36,37]

The findings of this study led us to believe that the existing framework for guideline development should be adapted to allow for a more systematic, sex-sensitive approach. The following recommendations were derived from this study's findings and those of the expert meeting. We submit them for consideration by guideline organizations and guideline developers.

Recommendations

First, the balance between men and women in guideline committees should be considered a mat-

Table 5. Recommendations for Focusing on Sex-Related Factors in Guideline Development[a]

Formulation of initial key questions (and subquestions)
Guideline developers should:
Make an assessment to determine if there are any plausible reasons for anticipating differential relative effects for both sexes. If so, make sure that the key questions are formulated clearly to facilitate a review of the literature.
Development of search strategies
Guideline developers should:
Make sure that search strategies are capable of detecting evidence (both direct and indirect) that supports or refutes any hypothesized differential effects.[b]
Appraisal of scientific evidence
Guideline developers should determine whether:
The studies they review are well designed.
The study population is stratified and whether it is sufficiently large for an analysis of differential effects on the basis of sex.
The relevant subgroup analyses have been carried out correctly (in key studies).[c]
Sex is a modifier for the research outcome.
Formulation of recommendations for the guideline
Where appropriate, guideline developers may consider the following questions when formulating recommendations:
How likely is it that the results of published research are applicable to both men and women?
How likely is it that differences in baseline risk would result in differential absolute effects?
How likely is it that there are important differences in tradeoffs between any anticipated harmful and beneficial effects?
Do any of these considerations warrant the use of different recommendations?
Composition of the guideline document
Guideline developers should have prior knowledge of the various ways in which sex-related factors can be represented in guidelines:
When evidence has been found.
If differences were expected but no evidence was found.
If no information is available.
Selected sex-related factors may be mentioned in various subsections of the document:
Throughout the text.
In specific paragraphs.
In a subsection on special populations.
In footnotes.
It is useful to reflect on the advantages and disadvantages of each option before drafting the guideline.

[a]These recommendations are suggested by this study and by other data.[38]

[b]Sex-specific search terms used in this study may be useful to search for direct evidence (Table 3). The requisite individual sex-specific search terms should be combined with one another using the Boolean operator OR, and used as a group—combined with the rest of the search strategy—using the AND operator.

[c]Several publications provide useful information on the methods involved.[39,40]

ter of routine. Second, guideline organizations should do more to motivate guideline committees to address sex-related factors. They could do so by providing these committees with specific examples showing how the quality of guidelines can be improved by consideration of the sex of the patient population. Third, guideline organizations should make efforts to provide guideline committees with the technical support needed to facilitate considerations of sex-related factors at every stage in the process of guideline development. These stages involve the formulation of initial key questions, the development of search strategies, the appraisal of scientific evidence, the formulation of recommendations for the guideline, and the composition of the final guideline.

Table 5 contains suggestions about the methods that guideline developers could use when focusing on sex-related differences and similarities (sex-related factors) in the stages in the process.

CONCLUSIONS

In recent years, an increasing number of studies have shown that there are marked sex differences in the conditions and patterns of health that affect both men and women. This study suggests that the standard methodology for the development of clinical guidelines does not facilitate a systematic approach to the assessment of available research evidence on the basis of sex. The lack of a systematic approach could cause relevant information on sex-related factors to be omitted from published guidelines. Ultimately, this could have adverse consequences on the quality of care.

Based on the results of this study, we have formulated a number of recommendations for guideline organizations. These could be incorporated into the standard procedures for guideline development to encourage a greater focus on sex-related factors. Our recommendations must be seen as a very first step. If these recommendations are to be implemented, additional work will be needed to develop an educational program and a set of practical tools for guideline developers. Additional research is needed to evaluate the practical value of this approach and its impact on published guidelines. The two organizations involved in this study (NHG and CBO) are currently participating in an intervention study, which aims to address these issues.

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