Sex differences in health research and clinical guideline development
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Chapter 7

General discussion
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In current medical practice, research based evidence is an important foundation for clinical decision making. Clinical practice guidelines are a major instrument for keeping physicians up-to-date about this evidence. In order to provide optimal care to both men and women, it is important that medical research provides sufficient sex-specific data regarding diagnosis and treatment. Also, this evidence has to be included in clinical guidelines so that it is easily accessible to physicians.

The objectives of this thesis were to provide insight into how sex differences are taken into consideration in health research proposals presented to the Netherlands Organization for Health Research and Development (ZonMw) and in the guidelines developed by two Dutch guideline development organizations, the Dutch Institute for Healthcare Improvement (CBO) and the Dutch College of General Practitioners (NHG).

This chapter summarizes the main findings of the studies presented in this thesis. Secondly, it offers some reflections on the methodology we applied in these studies and on our findings. Thirdly, it presents recommendations for research funding and guideline organizations, and for further research. The chapter ends with a summary of the main conclusions of the thesis.

Main findings

Encouraging Attention to Sex Differences in Health Research

Like health research funding organizations in North America, the Netherlands Organization for Health Research and Development (ZonMw) has developed a policy directed at facilitating attention to sex differences in health research. We found that research proposals submitted to a programme that provided specific instructions on how to consider diversity factors (ZonMw Prevention) more often expressed the intention to take sex differences into consideration compared to a programme that provided a more general set of instructions (ZonMw Innovation) (difference 13%; 95% CI: 3.1-22.9) (Chapter 2). However, a considerable number of research proposals in both programmes failed to take sex differences into consideration, even though this might have been relevant. We concluded that the instructions given by ZonMw provide incentives that are still insufficient for researchers to describe if or how they are planning to pay attention to sex differences in their research.
ATTENTION TO SEX DIFFERENCES IN GUIDELINE DEVELOPMENT

The study presented in Chapter 3 examined the way in which Dutch guideline organizations address evidence on sex differences in their guideline development methodologies. It showed that there was no systematic attention to this issue in the different steps of guideline development: of the seven guidelines we assessed, none included a question (or sub-question) focusing on sex differences; no sex-specific search terms were used to identify relevant research publications; and the procedures used for critical appraisal of the literature did not include any systematic focus on sex-specific factors or effects. A lack of awareness and know-how among guideline developers were identified as some of the main barriers to systematic attention to sex differences in guideline development. To improve this, ZonMw offered us the opportunity to design an implementation project: the diversity consultation project. A toolkit and a corresponding training course were developed to improve awareness concerning the relevance of considering sex differences in the guideline development process, as well as the competence and skills necessary for putting this into practice. The training course was based on the principles of adult learning. A post-course evaluation showed that the participants (staff members of the guideline organizations) rated the training course positively on content, programme, and trainers. Written comments suggested that the course had met its objectives (Chapter 4).

We evaluated the effect of this intervention, combined with a second intervention (regular contact between a gender expert and staff members) using a quasi-experimental design with an intervention group (six guideline committees) and a control group (Chapter 5). Our pre-post evaluation revealed that the attitude towards the importance of paying attention to sex differences held by the members of the intervention group did not change significantly compared to those in the control group. Yet, guideline documents that were produced by the intervention group reflected more statements on sex-specific factors than the available previous versions. We concluded that education and expert feedback may increase the uptake of information on sex differences in guidelines.

In a next step, we observed 22 meetings of the six guideline development committees (GDC) that took part in our intervention group. In Chapter 6 we analysed the characteristics of discussion episodes on sex differences in these meetings and whether or not information from those episodes was reflected in the guideline text. We found that sex-specific data on reproductive issues were more often discussed and reflected in guideline texts than those on other sex-specific health issues. Discussion episodes initiated by chairpersons were most often reflected in the guidelines and those initiated by staff members were least often reflected. Overall this study indicated that GDCs that were guided by staff members who were trained in using our toolkit regularly focussed on sex-specific issues.
Reflections on the Methodology

In the five studies reported in this thesis several methods have been used to answer the main research questions as provided in the introduction. These are: Chapter 2: a content analysis of research proposals; Chapter 3: open-ended interviews with key persons, content analysis of guidelines and expert opinion; Chapter 4: development and implementation of educational strategies, and questionnaires; Chapter 5: questionnaires and content analysis of guidelines; and Chapter 6: non-participant observation of guideline working group committees, qualitative analysis of the characteristics of the discussions and content analysis of guidelines. The strengths and limitations of these methods have been discussed in the accompanying chapters. Yet, several aspects of the research process warrant some further reflection.

Design of the Studies on Attention to Sex Differences in Guideline Development

This thesis includes four studies on attention to sex differences in guideline development. Together, the selected designs of these studies reflect some of the stages of a model for planning and evaluation described by Grol, which is commonly used in projects that aim to improve the behaviour of health professionals. Using a descriptive and explorative design, the first study (Chapter 3) had the aim of collecting baseline evidence on the current approach to sex differences in guideline development and on factors that may facilitate or inhibit guideline developers’ preparedness to change. The second study focussed on the development of an intervention (Chapter 4). Based on the theory of behaviour change in professionals and on information from the first study, we developed a toolkit and a course. An initial qualitative approach was used to evaluate whether these interventions met the objectives. The third study was experimental in nature (Chapter 5). We set out to test the hypothesis that the groups that had been exposed to the interventions (educational and expert feedback to staff members of guideline development committees) would demonstrate a more positive attitude towards the consideration of sex differences in guideline development than a control group. To this end we used a quasi-experimental design. In the fourth study (Chapter 6) we used an observational design in order to examine how groups that had been exposed to the interventions actually implemented the suggested approach in their work.

In carrying out these steps, we realized that implementation projects do not always run completely according to plan, a phenomenon that has been observed earlier. In our case, it appeared to be difficult to apply the quasi-experimental design completely. It turned out that CBO had invited all consultants (including the ones we had assigned to the control group) to participate in the training course. This may have affected our findings, as is discussed in Chapter 5. Another factor may also have influenced the reported attitudes of the group members. At the start of our project, there
had been a public debate in the media and in the Dutch parliament in which concern was expressed about the lack of attention to the ethnicity of patients in NHG guidelines. It is possible that this debate has made guideline developers more aware of the importance of attention to specific characteristics of the target groups of guidelines, including their sex. Nevertheless, we feel that the different studies provide an adequate evaluation of the different stages of the project.

**Content analysis**

In four of the five studies included in this thesis a descriptive evaluation, arrived at through content analysis, was used to explore how attention was given to sex differences in research proposals and guidelines. The strength of this approach was that it provided insight into how sex differences are addressed in documents that play a key role in practice. A major challenge using this method was how to develop a valid and reliable instrument that yields the same results in different trials. As the method sections in the previous chapters are short, we would like to provide a more comprehensive overview of how we tried to meet this challenge.

In line with methods that are commonly used in content analysis, for the study described in Chapter 2 we took the following steps: we developed an initial comprehensive list of concepts that could be potentially relevant to identify statements referring to men, women, sex differences, etc. Using this list, in the first round of the document analysis the researcher read the full documents to identify any relevant passages referring to sex differences. This exercise also permitted the researcher to add concepts that appeared to be a relevant extension of the initial list terms. As an extra step, to verify the results of the manual content analysis, a second digital analysis using predefined terms was performed in which the search and find function was used to determine the presence of concepts in the documents.

In the content analysis of guidelines the first two steps of the content analysis were performed in a similar manner (chapters 3, 5 and 6). For the research reported in Chapter 3, the verification of the first round of the content analysis of the guidelines was performed by the same researcher. In chapters 5 and 6, verification of the content analyses were performed by independent second persons.

**Subjectivity in data collection**

In some of the reported studies, the researcher was the instrument for data collection (e.g.; in Chapter 2, interviewer; in Chapter 6, observer). In contrast to more objective methods of data collection, in this approach the subjective considerations of the researcher may play a role. The researcher was aware of this issue; she saw it as her task to be an impartial research instrument. Her research aim was to discover how sex differences were addressed in research proposals and in guideline development. This meant that she did not try to look at researchers’ writing proposals or at guideline developers as
individuals who were doing something right or wrong with respect to the consideration of sex differences. She was interested in the processes. Thus, she intended to record the data in a fair and non-judgemental way. Moreover, the analysis of observational and interview data were checked by other researchers or data sources. Although subjectivity can never be completely ruled out, we believe we have adequately dealt with this problem.

Generalization of the findings
The studies presented in this thesis are performed in Dutch organizations. However, research evidence regarding sex differences in health is applicable to patient populations in most countries, not only to those in the Netherlands. In addition, the Dutch guideline organizations apply an internationally accepted standard methodology for guideline development. For these reasons, the recommendations formulated to enhance the consideration of sex differences in guideline development seem also to be of relevance to other, international organizations.

Our study on the effects of incentives to promote attention to sex differences in health research by the Dutch health research funding organization adds comparative material for studies of such programmes within other international health-funding organizations.

Reflections on the findings

Institutional context
The studies in chapters 3-6 in this thesis focussed on the work of guideline development groups. It should be acknowledged, however, that organizational policies and practices of the guideline organizations are an important overarching framework for the actual work of committees. Therefore we would like to provide some additional information on how these organizations reacted to the diversity consultation project, based on observations during informal meetings and interviews with staff members. These observations revealed that both organizations were taking responsibility for this project. This is exemplified by the following actions:

First, each organization appointed one of their staff members to act as the contact person for diversity issues within the organization. Besides sex-related issues, this staff member was also charged with the task of ensuring that other diversity issues, such as ethnicity and socio-economic status, would receive attention in guideline development.

Secondly, a chapter on attention to ethnicity and sex differences was included in the new handbook for guideline developers, which was a publication common to both organizations. Thirdly, the clinical librarians of both organizations used the search strategy for identifying sex-specific information in bibliographic databases, which was developed for our handbook and toolkit as a standard tool for searching the literature. Fourthly,
CBO has included some of the elements of the course we developed for the diversity consultation project in its existing course on Evidence Based Guideline Development (EBRO) \(^{10}\). This course is taught to all (new) members of their guideline committees and staff. Finally, staff members of each of the organizations gave a workshop with a member of our project team on how to address sex differences in guideline development at two international conferences on guideline development (the European General Practice Research Network Conference 2007 in Nijmegen, The Netherlands and the Guidelines International Network Conference 2007, in Toronto, Canada).

This organizational back-up may have facilitated the acceptance of the approach proposed by our project. However, we also observed some barriers: firstly, in the development of our toolkit and training course, we assumed that all guideline developers were familiar with the basic skills for evidence based guideline development. However, as other studies have found, in our studies we observed that some members of guideline committees lack those skills \(^{11}\). This is of course an inhibiting factor for the development of evidence based clinical guidelines in general \(^{12}\). And, in the case of this project, it also made it difficult for trained staff members to transfer what they had learned in the course to some of the group members. Secondly, most staff members of guideline organizations and members of guideline working groups perceived the need to take sex differences into consideration in their work not as a normal duty but as an extra one, which would take additional time. Having to do extra work was seen as a barrier to implementing a gender approach to guideline development. One obstacle is that there is only a limited amount of time and funding available for the development of a guideline. As GDC members are busy people and participate on a voluntary basis, another obstacle was that some consultants were reluctant to ask them to make an additional time investment.

**Previous research**

Current national policies, such as the Equality Impact Assessments for the employers of the National Health Service in the United Kingdom, and international treaties of the United Nations \(^{13},^{14}\) call for attention to sex differences in guideline development. Consideration of the specific characteristics of a guideline’s target population, including sex and gender characteristics, is also seen as a quality criterion for guideline development \(^{15}\). In recent years a number of toolkits and guidelines have been developed for paying attention to specific characteristics of patient populations in guideline development \(^{16},^{17}\). However, thus far none of these toolkits and guidelines have addressed the issue of sex differences. Indeed, a unique contribution of this study is not only that it developed such a toolkit, but also that it evaluated its impact in practice.

However, even if guideline committees are willing and able to consider sex differences, guidelines are primarily research based. This means that publications of high quality studies on sex differences in health must be available. To contribute to this, health
research funding organizations have been stepping up their efforts to enhance attention to sex differences in health research. However, the study presented in Chapter 2 confirms the conclusions of other studies that such efforts have a limited effect, especially if they fail to put clear demands on researchers. For that reason, the United States National Institutes of Health (NIH) and the Office of Research on Women’s Health have taken additional initiatives in their gender policy such as the provision of clear instructions on application and evaluation forms for research projects and the education and training of NIH staff members, applicants and evaluators of research projects and researchers 18, 19.

SEX DIFFERENCES IN REPRODUCTIVE HEALTH AND OTHER AREAS OF HEALTH

Traditionally, research on sex differences was mainly limited to the area of reproductive health. In recent decades more research on other than reproductive health related issues has been published. Examples of the latter are given in the introduction. We found that the guideline committees that participated in the diversity consultation project paid much more attention to sex differences in reproductive health than to those in other areas of health, both in their discussions and in the guidelines themselves. As was pointed out in chapters 5 and 6, one explanation may be that high quality research on sex differences in other than reproductive health issues is still not readily accessible or available. Another explanation may be that the diversity consultation project was more successful in reinforcing the traditional, narrower approach to sex differences, focussed on reproductive health, than in encouraging a new and wider approach focussing on broader health related issues. These hypotheses require further research.

It is our contention that the quality of guidelines may benefit from the wider approach to potentially relevant sex-specific characteristics of the patient population 20. This is not to say that the narrower approach focussed on reproduction-related sex differences is not important: to the contrary. Questions related to the impact of medication on fertility and pregnancy are now being investigated routinely in pharmaceutical trials. In our opinion the results should also be routinely reported in guidelines, whether positive or negative, as this could guide decision making by both physicians and patients. One example of good practice is the most recent US guideline on asthma. Recent studies have shown that poorly controlled asthma in pregnant women can lead to increased prematurity, need for a caesarean delivery, preeclampsia, growth restriction, and maternal morbidity and mortality 21. Based on this information the guideline states: “It is safer for pregnant women with asthma to be treated with asthma medications than it is for them to have asthma symptoms and exacerbations” 21. Another example comes from the recent CBO Guideline on rheumatoid arthritis. It clearly states that evidence has shown that the use of a specific medication (sulphasalazine) may lead to reversible infertility and to impaired motility of sperm in men 22, 23.
Recommendations

In its report, *Exploring the biological contributions to human health: Does sex matter?*, the Institute of Medicine stated: “Until the question of sex is routinely asked and the results—positive or negative—are routinely reported, many opportunities to obtain a better understanding of the pathogenesis of disease and to advance human health will surely be missed” 20. The studies presented in this thesis suggest the following recommendations on how health research funding and guideline organizations, and researchers may contribute to this.

**Health research funding organizations**

Firstly, in order to help applicants understand what is expected from them, they must be supplied with a clear set of instructions on why and how to address sex differences in their research plan. Secondly, it should be made clear to applicants that the reviewers of their research proposals will be carrying out specific checks to determine whether sex differences have been appropriately addressed. Thirdly, initiatives should be launched to provide appropriate training for the staff of organizations that fund health research, as well as for present and future applicants and reviewers. The training in question should address issues such as the relevance of focussing on sex differences in health research, and give examples of how this should be done. Fourthly, as with any policy, progress should be monitored regularly, and clear indicators are needed in order to measure progress.

**Guideline developing organizations**

Firstly, it should be recognized that it cannot be taken for granted that guideline development committees pay systematic attention to sex differences in the process of guideline development, since this requires specific knowledge and skills. Secondly, if systematic attention to sex differences is seen as a relevant quality issue for guidelines, it must be recognized that this issue requires attention from the very beginning of the guideline development process (key-questions) until the very end (formulation of recommendations). Thirdly, the framework that has been developed and evaluated in this study (toolkit, training course and expert feedback) may encourage systematic attention to sex differences in guideline development. Besides being relevant to the training of staff members of a guideline developing organization, this framework may be used to train other stakeholders in the process of guideline development, such as the group leaders of guideline development groups and the other members.

In the course of this study it became apparent that there is still a lack of research based evidence on sex differences in many areas of health. Because of their focus on evidence, guideline development committees and guideline organizations are in a good position to register these gaps. These organizations should consider it their tasks
to provide recommendations for future research on sex differences, for instance to public organizations for the funding of health research.

Like the Dutch guideline organizations that were the focus of this study, guideline organizations in many other countries are also using an internationally accepted methodology for guideline development. The Appraisal of Guidelines Research and Evaluation (AGREE) collaboration, the developers of an appraisal instrument to assess the quality of guidelines, and Guidelines International Network (GIN) have become a main platform for discussing important methodological issues for guideline development, and for setting criteria for the quality of evidence presented in the guidelines and the strength of recommendations. In order to advance attention to sex differences in guideline development and further the development of its method, it might be relevant to initiate an international discussion within the AGREE collaboration and GIN.

Globally, the World Health Organization (WHO) has provided guidelines for guideline developers, in which recommendations on how to address sex differences in guidelines are still lacking. In line with WHO’s commitment to gender equity, it would be relevant to add specific recommendations on how to apply a gender perspective in guideline development.

**Future research**

To advance the gender policies of health research organizations, their accomplishments should be regularly monitored by the organizations themselves or by independent researchers. To this end indicators for the success of such policies need to be developed and tested. To monitor attention to sex differences in guidelines, the development of a specific screening instrument is recommended. The toolkit developed in this project can be taken as point of departure.

Also, further research is needed on the effect of psychosocial processes in guideline development groups on the attention to sex differences in guideline development.

This study and its recommendations focus on sex differences. It has been argued that other differences within and between patient populations, such as ethnic, socio-economic and age differences are also an overlooked dimension in health research and guidelines. This requires further research. The models used in this study can be a relevant point of departure for such studies.
GENERAL CONCLUSION

This thesis provided insight into how attention is paid to sex differences in health research proposals presented to a Dutch health research financing organization and in clinical guideline development by two Dutch guideline development organizations. The following main conclusions can be drawn.

Sex differences are not yet considered in health research proposals in which this might have been relevant. Therefore, efforts to enhance the consideration of sex differences in health research proposals are still needed. This implies that the current incentives used by ZonMw need to be amended.

Two main guideline developing organizations in the Netherlands did not consider sex-related issues systematically during guideline development at the onset of this project (2002). During the past six years their consideration of sex-related issues in guideline development has been enhanced and both organizations are making efforts to further improve this attention. Follow up research will be needed to further enhance the consideration of sex differences in health research and guideline development.

This thesis provides recommendations on how to enhance the consideration of sex differences in health research proposals, and an extensive framework and recommendations for the uptake of sex-specific evidence in guideline development. The recommendations and the framework may be of use for the further development of strategies with the aim of enhancing the consideration of sex differences in health research and clinical guideline development.
REFERENCE LIST


