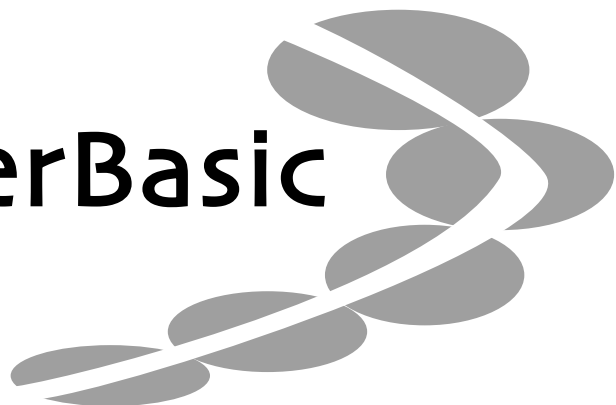


**Proceedings GenderBasic Expert Meeting
Promoting integration of sex and gender in
biomedical and health related research
January 26-27, Maastricht**

Madelief Bertens, MSc MA, Project officer
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GenderBasic



Proceedings GenderBasic Expert Meeting: Promoting attention to sex and gender in biomedical and health related research (Maastricht, January 26-27, 2007)

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Proceedings GenderBasic Expert Meeting

Promoting integration of sex and gender in biomedical and health related research

January 26-27, Maastricht

An Expert Meeting was organised as activity of GenderBasic (EU FP6 Women and Science Specific Support Action). The meeting was held on January 26-27, 2007 in Maastricht, the Netherlands*.

Background

Integration of the gender dimension in biomedical and health related research consists of the consideration of both sex differences and differences resulting from gender (Klinge & Bosch, 2001. *Gender Impact Assessment of EU FP5 Life Sciences Research Programme Quality of Life and Management of Living Resources*). Biological and socio-cultural differences between women and men may result in different epidemiological patterns and effect modification of diagnostic, preventive and therapeutic interventions. It implies that in specific research projects the focus of attention driving the research questions can be on sex differences, on effects of gender or on the interaction between the two.

The EU Sixth Framework Programme (FP6) guidelines comprise a set of specific questions concerning integration of the gender dimension. Life sciences projects funded by FP6, had to meet the following criteria:

- Research proposals must include a description of how attention to sex and/or gender differences will be integrated in the content of the research.
- Research consortia must report on the implementation of these plans in progress reports to the Commission.

Applying the FP6 guidelines to biomedical and health related research is not without difficulty and will pose different challenges (practical, methodological, conceptual, ethical and financial) to basic, translational, clinical or public health research. It seemed that basic life sciences research involving cells, tissues, animals and other materials, encountered a variety of problems.

Objectives of GenderBasic Expert Meeting

Objective of the GenderBasic Expert Meeting was to provide scientists involved in health related research (with a focus on basic and clinical research) funded by the EU Framework Programmes, practical tools, relevant examples and best practices regarding paying attention to sex and gender differences in the content of their research. Ten reviews have been commissioned, which together cover various conceptual issues and methodological aspects of paying attention to sex and gender in research as well as six health areas where attention to sex and gender issues is urgently called for. The methodological reviews addressed basic, translational, clinical and public health research. The identified health areas were: anxiety disorders, asthma, metabolic syndrome, nutrigenomics, osteoporosis, and work-related health.

The reviews were meant to provide the state of the art regarding specific problems and opportunities or challenges, and proposing widely supported solutions. The reviews, referee comments and discussions contributed to answering the following questions:

- What is the state of the art regarding the integration of attention to sex and gender issues in the methodologies of basic, translational, clinical and public health research?
- What do we know? Which gaps in knowledge can be identified that deserve further research?
- What is the state of the art regarding the integration of sex and gender aspects in selected health areas identified as in urgent need of addressing sex and gender factors (anxiety disorders, asthma, metabolic syndrome, nutrigenomics, osteoporosis, and work-related health)?
- What do we know? Which gaps in knowledge can be identified that deserve further research?
- Which tools do researchers need to ensure a better integration of sex and gender aspects in their research?

* The expert meeting was chaired by Peggy Maguire, Director General, European Institute of Women's Health. Minutes and notes were taken by Bart Penders, Maastricht University, Faculty of Health, Medicine, and Life Sciences, Dept of Health, Ethics and Society.

For the list of all expert meeting participants, see page 59

Expected Results

- Tools to be used by EU services, researchers and research evaluators for the improvement of attention to the gender dimension in biomedical and health related research.
- Recommendations on further implementation of the gender equality policy for research in the EU 7th Framework Programme (2007-2013).

High profile researchers were invited on the basis of their expertise and proficiency to participate in the Expert Meeting, resulting in an assemble of researchers from a variety of disciplines (basic researchers, clinical researchers, epidemiologists, social scientists, gender researchers) with an interest in addressing sex and / or gender issues in research.

Procedure

These proceedings are a report of the discussions held at the Expert Meeting. The document brings together the abstracts of the reviews, the written comments¹ and an overview of the discussions that took place, organised into the guiding questions we provided authors and reviewers for their writing and reviewing task. Those questions were:

- What is the state of the art regarding integration of attention to sex and gender issues in the **methodologies** of basic, translational, clinical and public health research?
- What are **sex and gender differences** within the different selected health problems (anxiety disorders, asthma, metabolic syndrome, nutrigenomics, osteoporosis, and work-related health) and the consequences for diagnostic, preventive and therapeutic interventions?
- What are the **conceptual and theoretical challenges** regarding integration of attention to sex and gender issues in basic, translational, clinical and public health research?
- Which **practical tools** do researchers need to ensure a better integration of sex and gender aspects in their research?
- What are the **ethical and financial difficulties** concerning integration of sex and gender in biomedical and health related research?
- What are the **implications** for research and policy **recommendations**?

For this report the presentations and discussions of the papers during the expert meeting were transcribed, entered, coded and analysed using Nvivo 2.0, a software package for analysing qualitative data.

In a separate document the full review papers, the comments and the power point presentations given at the meeting will be brought together. The format of this document is still under discussion and, among other things, dependent on a future successful publication of the reviews. The power point presentations have been made immediately available after the meeting (www.genderdiversiteit.unimaas.nl/genderbasic).

The draft proceedings were sent for comments to all authors and reviewers². The summary of organised salient discussion points contains a section on remaining questions and preliminary recommendations. This section will serve as basis for the final recommendations that will be drafted in consultation with the Commission and interested authors and reviewers.

Sex and gender in biomedical research

“Sex” and “gender” are terms that have a variety of connotations and definitions and are applied according to the different fields of research. In these proceedings the discussion will be depicted using the vocabulary and terminology the participants used during the discussions. However, the participants used some terms, i.e. sex and gender, in a confounding manner. Generally speaking, we have chosen to use the following definitions of sex and gender:

- Sex refers to biological characteristics as chromosomes, physiology and anatomy that distinguish females and males.
- Gender refers to the array of socially constructed roles and relationships, personality traits, attitudes, behaviours and values that society ascribes tot the two sexes on a differential basis. Gender is relational; gender roles and characteristics do not exist in isolation but are defined in relation to one another (Klinge & Bosch, 2001, Gender Impact Assessment, FP5, QoL pg 32).

¹ Please note, the comments have been written by the reviewers as a discussion paper and, as such, some statements are not referenced in the manner they would be were it a scholarly paper. Furthermore, some of the commentary has been limited to comments which contributed to the discussion. Comments related to stylistic, grammar or spelling issues in the paper have been left out in these proceedings.

² We received comments and have corrected the draft with comments from Anita Holdcroft, Flavia Franconi, Dirkje Postma, Susan Phillips, Vera Regitz, Elizabeth Zemp-Stutz, Anne Hammarström, Monique Frings-Dresen, Jose Ordovas, Nicolien Wieringa. Onno van Schayk, Edwin Mariman, Pirooska Östlin, Janneke Mens-Verhulst and Marrie Bekker consented. We received reactions without any comments on the writing, from Piet Geusens, Alan White, Agnes Wold and Eva Swahn.

Comprehensive summary of salient discussion points from the GenderBasic Expert Meeting

During the GenderBasic Expert Meeting several salient discussion points and recommendations surfaced, some of which could be expanded on in a following workshop or meeting. These deliberations are summarized in bullet points in this short memo. These points are the groundwork on which final recommendations will be based. Disease-specific discussion items are stated at the end of discussion of each paper.

1. Impressions of the participants:

1.1. GenderBasic

- GenderBasic put gender on the agenda; agenda setting as an objective is accomplished.
- GenderBasic was nominated as a “Star-project”. However there is some concern about the continuity of the project.
- GenderBasic is novel project, very promising, and the participants are enthusiastic.
- Advice for GenderBasic: start a green paper debate (for the commission).

1.2. Expert meeting was

- “Nice and elucidating”
- “Unique” and the subject of gender in biomedical and health related research “Intriguing”
- “Innovative”
- Meeting “elicited reinforced excitement”.
- Some participants felt an imbalance between the biomedical and more socio-cultural models; the biomedical research paradigm was overrepresented in the meeting.
- Missing topics in the meeting were consequences of behaviour for health conditions, practical implications and implementation possibilities.
- Most participants came from Northern Europe; more researchers from Eastern and Southern Europe should have been included.

2. Integration of sex and gender in biomedical and health related research

2.1. Conceptual and theoretical issues of sex and gender in research

- Definitions of the following concepts were not consistent in the review papers and among participants. The terms should be clarified in order that everyone uses them in the same manner with the same definition.
 - Sex and Gender
 - “Gendered research” (f.e. paper 8)
 - Masculinity and Femininity
 - Environment (biochemical environment vs. socio-cultural political environment)
 - Tool: e.g. algorithm, model, classification
- Understanding and agreements on these concepts could aid in operationalisation of these concepts.
- Participants were both impressed and worried about the complexity of the concept of gender.
- Concern: Many researchers state to be studying gender, but in fact they are studying sex differences, this should be clarified.
- Various fields and disciplines of research focus on diverse topics, and there was debate on how these differed in outcome and function:
 - Sex and Gender
 - Sex differences research vs. gender research.
 - The nature-nurture debate continues, also on how these interact.
 - Symptoms versus behaviour debate.
- These debates are on biological and social aspects of health related research and should be distinguished.
- Gender and sex (and the interaction between gender and sex) play a role on molecular/genetic level but also on a population level.
- The term “gendered” as a positive (e.g. taking a gender perspective in research), but also negative (e.g. meaning influenced by stereotypical gender roles or processes) concept.

- Sex difference research
 - On a biological, descriptive level, definitions are needed on differences between males and females.
 - Sex differences are closely related to sex hormones and especially estrogens
 - The effects of estrogens are both negative and positive for health.
 - Despite all the sex difference studies, there still is a necessity to provide more baseline information on biological sex differences.
 - Basic research shows us where the sex differences come from, but where do we go from here?
 - Findings from sex-difference research should be linked to clinical importance.
 - Participants were positive about the research conducted about differences between the sexes, but attention should also be paid to within-sex differences.
- Gender research
 - Researchers should be aware of the distinction between sex and gender: need for more gender research.
 - Instead of only describing sex differences, we need to focus on understanding how gender works.
 - Even on a laboratory level do animals have a socio-cultural environment, which needs to be considered in research.
 - Gender is heterogeneous, diversity goes beyond gender.
- Candidacy and Yentle-syndrome (referring to the neglect of the other sex if a condition is labelled as 'female' or 'male' disease).
 - Because some diseases and health issues are more prevalent in either men or women; the research focuses primarily on one specific sex (e.g. osteoporosis, asthma, metabolic syndrome).
 - Gender and sex difference studies should not only focus on women, but also on the understanding of masculinity.
 - Men's health is a two-sided debate: Due to socialization men exhibit more risky behaviour and are more prone to for example suicide and alcohol abuse.
- Theoretical issues
 - On a biological, descriptive level, pathways and models of how sex and gender interact need to be studied.
 - Correspondence/dialogue should be improved to link biomedical research and social research.
 - Social scientists feel dominated by biomedical researchers.
 - Perhaps new models or paradigms need to be developed to understand and study sex and gender.
 - Intersectionalist approach could be applied: there is more than only gender. Real diversity research takes into account age, socio-cultural differences, sex, gender, ethnicity, and economic parameters.
- Many disciplines are involved in gender research. Multidisciplinary research is recommended.
- One of the returns of the meeting was that gender is taken seriously in research.

2.2. **Methodological challenges to integrate sex and gender in research**

- Regarding integration of sex and gender in biomedical and health related research, certain methodological aspects need to be considered:
 - Design
 - Stratification of males and females.
 - Sex is not a homogenous category.
 - Need to account for intra-group differences; the diversity aspect.
 - Instruments
 - Techniques
 - Measures
 - Confounders
 - Variables, which variables to include and whether sex is:
 - Effect moderator
 - Binary variable
 - Explanatory variable
 - Independent variable
 - Multilevel variable
 - Statistics
 - Interaction terms
 - Co-variance
 - Power issues: number of animals, or number of respondents

- Miscellaneous
 - Methodological problems need to be solved to be sure about valid conclusions.
 - Conceptual and statistical complications issues need to be addressed.
 - Validity of concepts needs to be integrated in models.
 - The benefits from using interdisciplinary teams are acknowledged.
 - Researchers should keep the panoramic view: combine the genome-proteome-environment in studying sex en gender.
 - The interface between nature-nurture needs more attention.
 - Sex versus gender research: what was presented in the meeting was mainly sex difference research. Both sex-difference and gender research are important but should be considered separately.
 - Tools for implementation of sex-difference findings and operationalising variables are needed.
 - Need for more longitudinal research, which will be expensive but worthwhile.
 - Need for more effect evaluation of interventions based on sex differences.
 - On the laboratory level: Guidelines are needed, like “Good Laboratory Practice”.
 - Good practices and normative issues need to be described regarding integration of sex and gender on the laboratory level.

2.3. Ethical and financial challenges

2.3.1. Regulations

- There was some discussion on whether to focus on equality or equity, what are the goals and with what means should we achieve these goals?
- We should strive for equity, whatever the differences are between the sexes.
- More research needs to be done within gender and not only on sex difference studies.
- Ethics concerning animals in laboratory research should be considered, especially within stratified research where the number of female animals is exponentially large.
- Concerning animal models, the question is whether the results are transferable to humans.
- Responsibilities of the researchers, institutes, implementers need to be addressed.
- Advice for GenderBasic was to start a green paper debate (for the commission).
- Attention to gender needed with medical research ethics committees.
- EC Ethical review: gender should be introduced.

2.3.2. Financial consequences

- Funding: the pharmaceutical industry seems reluctant to fund gender based research.
- Commercial issues need to be regarded (e.g. which population will benefit from a new medication).
- Expenses: stratification between the sexes implies a larger study population.
- We have some answers but we need to build tools, which will cost money.

2.4. Practical tools needed to integrate gender in research

- First of all the definition of “tool” needs to be clarified: e.g. algorithm, model, classification.
- Further the use of the tool needs to be explained
 - in basic, translational, clinical and public health research.
 - regarding consequences for diagnostic, preventive and therapeutic interventions.
- Tools are needed for implementation and operationalising of variables.
- Practical implications and implementation possibilities from basic science results.
- Tools for bridging biomedical and socio-research are needed.
- Researchers seem to be more and more aware of difference between sex and gender, but lack tools to integrate different levels.
- Protocols are needed on the biological, descriptive level.
- Guidelines are needed on laboratory level.
- A tool could be developed consisting of a list of conditions or guidelines, a decisional chart, protocol for different syndromes, about number of animals to be used.
- Gender index could be developed as a tool.

3. Remaining questions and preliminary recommendations

3.1. Implications for further research

- More research needs to be done within gender.
- There still are plenty of genes to be studied, just like other biological sex differences.
- Need for gender mainstreaming (in research and peer reviews).
- Peer review process is necessary on all research aspects and in all fields (reviewing papers, journals, grants, clinical research, study design, animal research).

- Lobby for more gender integration in clinical/animal research.
- Call for new research models, models in pre-clinical studies.

3.2. Implications for treatment/health or clinical practice

- Take care not to focus on sex and gender differences when it lacks relevance in clinical practice.
- Strategies should be developed using a gender perspective in public health.
- Translate research findings to medical practice and health practice.
- Translate research findings to education and models.
- Practical implementation of the sex differences: we need to inform the public about diversity.
- Need for more research but also practical implementation of findings.

3.3. Multi- interdisciplinary approaches

- Dialogue between the different scientific backgrounds is a start; it needs to be continued.
- Gender is primarily a social/cultural and political concept; therefore the socio-cultural sciences should be involved.
- Gender research should be interdisciplinary.
- We should take the interdisciplinary research a step further.
- Researchers should stick to their field but work in multidisciplinary teams.
- Not only bottom-up but also top-down approaches are valuable.
- Suggestion for a next expert meeting: smaller interdisciplinary group about one topic/health problem/disease.

3.4. Policy making

- Not only is a gender perspective useful in research but also in communicating. scientific evidence in arguments in the policy debate.
- GenderBasic put gender on the agenda.

3.5. Good practice

- Finally we would like to pursue the construction of guidelines or a quality mark “Good Sex and Gender Practice”, comparable to “Good Laboratory Practice”.

4. Dissemination

- European Commission
- European Research Council
- Research Institutes
- Research Councils in member states
- Research financing bodies
- Publication of papers
- GenderBasic website
- GenderBasic tools for researchers
- Gender & Health research agenda
- GenderBasic network
- Translation to health & biomedical curricula

Paper 1

Integrating the dimension of sex and gender into basic life sciences research: methodological and ethical issues in research. A review of the problems and solutions in experimental studies.

Abstract

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The research process, from study design, selecting a species and its husbandry, through the experiment and analysis, publication and peer review, is rarely subject to questions about sex or gender differences in mainstream life sciences research. However, the impact of sex and gender on these processes has been recognised to be important in explaining biological variations and presentation of symptoms and diseases. The mechanisms for these effects lie not only in biological differences but also in environmental, social and psychological interactions. Unfortunately, laboratory research often imposes restrictions that are not present in a normal population. These are particularly related to ageing, socializing and reproduction and, although present in humans, are not systematically studied in the laboratory.

Methodological approaches to this present lack of a gender dimension in research include actively reducing variations through attention to physical factors, biological rhythms and experimental design. The hormonal milieu is another factor and although their genomic activity is well recognised, the more acute non-genomic effects of hormones may play a role in the development of small sex differences that can compound during the course of an acute pathological event. In addition there are now many exogenous sex steroid hormones and their congeners used in medicine, for example in contraception and cancer therapies, and these may further alter cellular activity.

Having determined that sex and gender are determinants of many outcomes in life science research then in order to embed the gender dimension into basic science research, it has to be broadly applied. One approach may be externally through animal ethical review boards and peer review of manuscripts where standardised questions can be asked about study design and analysis. In addition the relevance of laboratory models should be questioned in order to determine how best they can represent the age-related changes, co-morbidity and variations experienced by different genders in clinical medicine.

Comments³

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It is well known that gender differences have been historically ignored or sparsely studied. Nevertheless, women are major users of the health care system yet measures indicate that women's health and health care are suboptimal (Weisman, 1996). Women live longer than men, they suffer from more physical illnesses, especially acute illnesses and nonfatal chronic conditions, and use more medication (Verbrugge and Wingard, 1987).

³ These comments have been moderately edited by Madelief Bertens

In her excellent review, Dr. Holdcroft first discusses the meaning of sex and gender in accordance with the definitions proposed by the Institute of Medicine report (Wizemann and Pardue, 2001); the term sex is used when differences are primarily biological in origin and may be genetic or phenotypic; gender is used when referring to social and cultural influences. Social interactions and environment are also very relevant for laboratory animals thus they have important consequences in preclinical research. In this context, the importance of early life social interactions and environment should be further emphasized, considering for one that mothers behave differently towards their male and female pups (Moore and Moralli, 1979; Moore, 1986; Moore and Power, 1992) and also taking into account the influence of diet and pharmacological treatments (Barker, 2000; Godfrey and Barker, 2001; Hales and Barker, 1992; Armitage et al, 2004; Bagley and Hayes 1983). Experimental modification of intrauterine and postnatal environment is associated with long-term consequences (Barker, 2000; Godfrey and Barker, 2001; Hales and Barker, 1992; Armitage et al, 2004; Loizzo et al, 2006). Although developmental programming is strictly related to developmental plasticity, once induced, the organism has a reduced capacity to revert the developmental trajectory, making developmental programming almost irreversible (Batenson et al, 2004). For example, adult males born from mothers that had protein restriction diet during gestation, have a lower glucose tolerance (Sugden and Holness, 2002), which is associated relatively with insulin resistance and hyperinsulinaemia in males and with impaired insulin secretion in females (Ozanne and Hales, 1999).

Early life events, particularly a perturbed mother–infant relationship, have generally been recognized as important contributing factors for the development of psychopathology. Perinatal handling has a gender-dependent effect. Neonatal handled females, fail to adapt to exposure to chronic restraint stress, compared to non-handled females, while no such difference is found in males (Papaioannou et al, 2002). In the chronic forced swimming stress experiments, handled males have shorter immobility times, and higher plasma corticosterone levels, while the opposite is true for females. Furthermore, neonatal handling significantly decreases basal plasma corticosterone levels in both pre- and post-pubertal animals (Papaioannou et al, 2002). Thus, neonatal handling provides males with a greater capacity to actively face chronic stressors, while in the females it increases their susceptibility to express ‘depressive’ behaviour since they are unable to cope and adopt ‘passive, despaired’ behaviour (Papaioannou et al, 2002). Clinically, depression is twice as common in women as in men (Kendler, 1998). In women, the incidence of depression, which peaks during childbearing years, seems to be associated with cyclic hormonal changes (Sagud et al, 2002).

The opposite has been found when the effect of neonatal handling on the metabolic effects is studied. Neonatal handling of male mice produces an increase in body weight, elevation of triglycerides and cholesterol, elevation of fasting glucose and insulin (Loizzo et al, 2006), whereas females present only a increase in body weight (Franconi et al, 2006).

Gender differences in mortality, growth and susceptibility to diseases have been evidenced (Rosen and Bateman, 2004). Indeed, as an example, the Y chromosome is known to accelerate the growth and increase glucose metabolism in the uterus (Burgoyne, 1993). At birth, the growth curve and heart rate are different in males and females (Nagy et al., 2000), while sexual dimorphism in fat patterning starts at 5-7 years of age (Webster-Gandy et al., 2003). Male infants have lower leptin level than female infants, even if the differences are not as great as those observed in adults (Lönnerdal and Havel, 2000). This is not surprising because the genetic sex in turn controls the development of gonadal sex. The question is whether sex chromosome genes, which are present in different quantities in the genomes of males and females, might be expressed differently and cause sex-specific patterns of development and/or function. Male mammals possess genes on the non-recombining region of the Y chromosome (NRY), not present in females and encoding 27 distinct proteins, which might act to cause masculine patterns (Carrell et al, 1999). Alternatively, genes on the non-pseudoautosomal portion of the X chromosome (NPX), which are present in two doses in females but only a single dose in males, could cause sex-specific development because of such different dosages. These differences are balanced by X silencing. Nevertheless, a significant percentage of NPX genes escape inactivation, at least in humans (Carrell et al, 1999). Therefore, cells containing genes, which escape silencing, could express higher gene products and this could have important implications. As an example, the gastrin-releasing peptide is expressed in both active and inactive X chromosomes: elevated levels of this peptide are detected in smoking females and have been related to the increased risk of lung cancer observed in smoking women (Legato, 2003). Moreover, neonatal treatment of human preterm infants with indomethacin has long term consequences on cognitive performance measured in school-aged children only in males (Ment et al, 2006).

Answering the previous questions implies studying the relevance of non-hormonal events on gender issue, the possible different responses of embryos, foetuses and infants to maternal pharmacological treatments and their relevant consequences, for example in developmental toxicology. Furthermore, this point involves the influence of gender on premature infant care and treatment.

As suggested by Dr. Holdcroft, the onset of differences between females and males and their variability with age and the life experience (e.g. pregnancy, lactation) must be also investigated. I would like to encourage considering that the wide use of oral contraceptives creates another population to be studied either clinically or experimentally in view of the multiple oestrogen and progesterone activities (Craig and Murphy, 2007; Genazzani et al, 2006).

Furthermore, considering that many experiments are performed in vitro with cells, proteins etc, there is the need to know the source of materials, in particular their origin (male/female), the age of animals, the oestrous phase, parity etc. Importantly, many studies have been done using pharmacological concentrations of hormones and only one type of sexual hormone without considering the interplay between progesterone and oestrogen, hence the study of this cross talk must be encouraged.

In order to appreciate differences, more attention should be dedicated on gender differences in pharmacokinetics evaluating:

- The single administration route (Donovan, 2005): the possibility that the normalization of the dose for body weight or surface does not automatically optimize the therapy (Anderson, 2005).
- Pregnancy, in which huge variations occur in several physiological parameters (for example plasma volume, sympathetic and parasympathic systems). During pregnancy there are changes in the activity of some CYP isoenzymes in the liver (Anderson, 2005). Moreover, CYP enzymes are also localized in placenta (Anderson, 2005). As also stated by the author of the review, pregnancy can modify the pharmacodynamic response.
- The time required to return to the pre-pregnant status after the delivery regarding drug and physiological responses.

Lactation

CYP activity, whose expression is genetically determined, is largely modulated by environmental factors (inducers, inhibitors) and sex hormones (Rinn et al, 2004; Anderson, 2005). In addition, P450 gene inducibility, which occurs through transcriptional factors, is often sexually dimorphic (Yoshinari et al, 2001).

Actually, it is not yet elucidated whether gender influences specific organ metabolism. The topic is relevant because in some specific neurons, CYP can be high as, or higher than, in liver cells as in other organ cells, and can also possess a high sensitivity as environmental inducers (Miksys and Tyndale, 2002). Variations in activity, induction and inhibition of brain CYP enzymes can contribute to the inter-individual changes in drug responses, including those linked to gender as suggested for neurosteroids' synthesis and catabolism (Miksys and Tyndale, 2002).

Experimental design

This is another important point which implies the selection of the model. For in vivo studies, it will be important to have standard values for single urine plasma and blood parameters for male and female subjects, strains, age and hormonal cycle. This knowledge could contribute to a better evaluation of drug safety.

Moreover, it will be important to know the transferability of results to humans including co-morbidity. For example, NIDDM occurs either exclusively or more frequently in males (Clark et al, 1983). Consistently with this observation, obese Zucker diabetic females (ZDF) rarely exhibit hyperglycaemia (Clark et al, 1983; Peterson et al, 1990), although they have levels of obesity and insulin resistance comparable to males suggesting that female pancreas is less deregulated by insulin resistance. Gender differences are not limited to ZDF but involve inbred Cohen diabetic rats, an experimental model of diet-induced type 2 diabetes mellitus, where males have a lower growth rate and more severe glucose intolerance patterns than females (Weksler-Zangen et al, 2001).

Gender- Placebo Effect or Gender difference response to vehicle

The question of whether females and males respond differently to placebo administration has hardly received any attention (Franconi et al, 2007). At the moment, the issue is still controversial and largely understudied (Rickels 1965, Wilcox et al, 1992; Saxon et al, 2001; Compton et al. 2003; Pud et al 2006; Gear et al, 1999; Averbuch et al, 2001; Mencke et al 2004; Olofsen et al, 2005). Therefore, further investigations are needed, as gender specific placebo effects would have many relevant implications for pharmacological research. This is true especially for clinical trials performed in the absence of golden standards, and in those clinical situations (e.g., pain and cough) in which the placebo effect is commonly considered relevant (Eccles, 2006; Beecher, 1955).

Besides the issue is also important for experimental studies, which use vehicles and or sham operated animals because females and males could respond differently and this must be included in experimental design.

Hormonal interactions

The scenario of activity of sexual hormones is very complex depending on the receptor subtypes, tissue co-activators and repressors. The presence and co-localization of alpha and beta oestrogen receptors in the nuclei of some cells can have important implications for oestrogen activity because, if ERa and ERb have opposite actions, cells that express both receptors might respond to oestrogen in different ways depending on the ratio of ERa to ERb (Helguero et al, 2005).

Indeed, they influence many physiological functions beyond the reproductive one. Oestrogen affects insulin sensitivity that decreases for the first time in females at the time of menarche and a much more

profound decrease in insulin sensitivity is observed at the end of pregnancy (Kaaja and Poyhonen-Alho, 2006). Furthermore, sexual hormones participate to control the redox state of cells modifying activity and/or expression of antioxidant enzymes and of the systems that generate reactive oxygen species (Gragasin et al, 2003; Guetta et al, 1997; Wassmann et al, 2005; Borrás et al 2003; 2005).

It is important to set up methods for hormonal variations beyond castration, which implies surgery, generating stress, and gender differences in stress response has been already described (Curtis et al, 2006). Actually, the use of antagonists of hormonal receptors or inhibitors of their synthesis could provide more information.

Discussion

What is the state of the art as regards integration of attention to sex and gender issues in the methodologies of basic health research?

Small differences between the sexes that could influence treatment response are lost in the statistical population mean. Thus it is important to also take the within-population variation into account. Question is: how can we discover these small sex-differences using the current statistical methods? "Sex differences may cancel one-another out". Sex is a modifier; just adjusting for "weight" is not good enough. Many factors, such as age, body composition or size, life events, previous and actual diseases, may cancel out sex effects. At what ages do these changes occur? Outcomes vary if you use these factors like age as a continuous variable or a dichotomous variable (young/old).

Sex hormones, level of estrogens and the menstrual cycle are much more complex to consider, they may be active in multiple ways. "Females are so variable, that you cannot reach any results"; the effects are lost by using the statistical group mean. By reducing the variability or variance we may overcome this. In research, these oestrogen effects are often levelled out. In addition, research hardly considers the importance of progesterone, neurosteroids, hormones that vary during the oestrous cycles. The previous points indicate that the number of experimental groups in gender research should be increased because of the biological (i.e. hormones) and environmental effects (see below). This implies a big higher research cost. If it is not possible to study in all oestrous phases within one study, perhaps results from different labs could be compared. Guidelines are necessary. Moreover, it could be necessary to find an animal model that is similar to humans and that must include oral contraceptive use. Rodents, the most used animals in experimental research, are not a good example.

Contemporary animal models decrease the difference of studying female rats at one episode; we need different models with regard to female cycles. There is a lack of models incorporating female cycles. How can you model non-linear, interdependent, sex-related differences?

Sex hormones seem to be a moderator within the female population; they only influence diversity in women. On the other hand, levels of testosterone are not measured. We need to look at the sex hormones in its entirety. In these new models also sex-dependent 'programming' and sex-dependent placebo and nocebo effects need to be taken into account.

Environment must be also considered and this involves the animal housing that need further guidelines and/or recommendations keeping in mind that when females are housed together they will reach cyclical similarity. Synchronizing is a general outcome of females housing together, the mechanism is unclear; possibly due to olfactory mechanisms. "Rats live by their smell. In humans, mother-child relation relies on smell". Female mice housing together synchronize, but when you add a male mouse, the synchronization is a lot faster.

Other interdependent sex-dependent factors relevant in research are contraceptive use, critical lifespan periods, i.e. menopause, pregnancy, pre- en post-delivery period, and lactation periods. In humans, the use of contraceptives need to be studied more; i.e. the disparity between women who use contraceptives and those who don't. All of this is important in pharmacokinetics and pharmacodynamics.

What are sex and gender differences regarding basic science research?

Where are sex differences located? What are these differences? Where do they come from?

The physiology is different between the sexes. There are sex differences, but does basic science research also show gender effects? Very small differences between the sexes produce clinical treatment effects.

The interaction between sex and gender becomes apparent in so-called Yentle syndromes. Candidacy or Yentle syndrome, referring to the neglect of the other sex if a condition is labelled as 'female' or 'male' disease, are terms that are often appointed to diseases or syndromes with high prevalence or more

significance of the symptoms among one of the sexes, and therefore the syndrome and its symptoms are often invisible among the other sex. An example is the Irritable Bowel syndrome, which is more common, or more often diagnosed, among women than among men. Women also have more problems with constipation and use more over-the-counter-medication than men. Therefore Irritable Bowel Syndrome is mostly studied among females. Candidacy is more influential in clinical research than basic research; however some syndromes should be studied among both sexes to understand the underlying mechanisms.

The question is whether sex chromosome genes, which are present in different quantities in the genomes of males and females, might be expressed differently and cause sex-specific patterns of development and/or function.

What are the conceptual and theoretical challenges?

Sex and gender research focuses on different aspects, respectively on biological differences between the sexes, on the influence of socio-psycho-environmental influences, and on gender differences; a translation is needed to use these differences in actual practice. The terminology or use of the words sex and gender is not consistent.

Some languages do not encompass both terms. Life science researchers usually use sex differences as exchangeable with gender differences. "Sex" is a dichotomy; male or female, whereas "gender" is a continuum where male and female have blurred edges. Gender is psycho-socio-environmental. Sex and gender interact with one another on several levels.

"Until now women were invisible in science". In animal models most populations studied consisted of males. Question is 'How can you model non-linear, interdependent, sex-related differences?' Incorporating female menstrual cycles and sex hormones into these models is imperative yet complicated. We cannot assume a linear association, but rather a non-linear correlation.

Social interaction (or gender) is probably more influential than sex hormones. "Social interactions play a role at more basic levels". Social interactions between the animals, but also between laboratory conditions (e.g. caretaker, feeding the animals) and animals, are of influence. "What matters is the sex of those that handle the rats". "So gender is relevant at the most basic level".

Which practical tools do researchers need to ensure a better integration of sex and gender aspects in their research?

In the discussion researchers stated that there was a need for standards for each stadium of female cycle and for new models considering the sex hormones, and the interaction with other factors.

What are the ethical and financial difficulties concerning integration of sex and gender in basic science research?

"Small sex differences can be studied within one discipline, however as they receive more attention they become BIGGER and best to be studied multidisciplinary".

Considering measuring categories of females at different times of their cycle implies 4:1 female to male (e.g. an oral contraceptive study, a population based study). Funding will be difficult: "too costly". Furthermore we need to take into account other sex-related variables. Question is the number of variables to consider in conducting a proper study: age, reproductive cycle, and pregnancy, body size etc. The funding bodies have realised that medicine needs to be population based. So considering differences in hormonal cycles, means including more groups, this would increase expenses by 4-10 times.

We need to identify the advantages of doing work in different groups – because it will reduce variation – hence better results. It may be that we need to identify appropriate times/hormonal milieus rather than use a mixture of females.

Implications for research and policy recommendations

More attention should be paid to specific (i.e. menopause, pregnancy, pre- and post delivery, lactation periods). Relevant is the menstrual cycle and contraceptive use. In humans the use of contraceptives need to be studied more; differences between women who use contraceptives and those who don't, need to be examined. In order to appreciate sex differences, more attention should be dedicated to gender differences in pharmacokinetics. Emphasize the use of oral contraceptive and of TOC create additional populations and there is a need to find a good experimental model for that.

Standardisation of research and presentation of results is necessary to combine results of several studies. Another suggestion is peer review of study design.

Summary of main discussion points

- Considering differences in hormonal cycles, means including more groups, this would increase expenses by 4-10 times.
- Testosterone is also a sex hormone; studies are needed on the influence of testosterone on health related issues.
- Social interactions between the animals, but also between laboratory conditions (e.g. caretaker, feeding the animals) and animals, are of influence.
- Synchronization of menstrual cycles among females housing together (rats and women) – mechanism uncertain, perhaps due to olfactory mechanisms Synchronization changes when male is added to the group.
- Suggestions are made to discover small differences between the sexes, because these small differences may have to be combined, (additive/synergetic) effects, which will increase the clinical worth.

Paper 2

Gender differences in asthma development and progression.

Abstract

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Asthma is an inflammatory, chronic airway disease that has a higher prevalence in boys before puberty and a higher prevalence in females in adulthood. Due to the complexity of the disease, no straightforward single mechanism can explain gender differences found in asthma. It is likely that hormonal changes and genetic susceptibility both contribute to the change in prevalence around puberty. Intriguingly severe asthma is also more predominant in females. It has to be established whether this is a social, cultural, hormonal and/or genetic issue. Topics requiring further research are:

- Foetal lung development in interaction with hormonal factors, since it has longstanding consequences up to adult life in which females are more susceptible to smoking and not only develop asthma but also COPD, the third cause of mortality worldwide.
- Stratification of genetic studies on asthma for gender, since some polymorphisms are in particular related to asthma in females. Further studies on hormone-gene interactions and e.g. X-chromosome genes in relation to asthma and atopy.
- Cellular hormonal influences in asthma and atopy in relation with innate and acquired immunity in both sexes. This would not only benefit asthma but many other diseases that show gender differences in prevalence, severity and treatment response.
- Animal models investigating the observed differences between males and females and susceptibility to environmental and hormonal factors in relation to lung and immune development.
- Differences in treatment response in asthma. It is of prime importance to stratify each double blind study for gender and investigate treatment responses in females and males separately. This is true for both studies designed by investigators working in universities and for pharmaceutical industries.

Comments

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This is a very well written paper describing the available knowledge of gender differences in asthma development and progression. The focus of the paper is on biological and not on behavioural gender differences. It is not clear whether behaviour might play a role in symptom reporting by asthmatic patients or symptom interpretation by the responsible physician. This cannot be excluded.

The paper describes in great detail the possible role hormones might play in explaining gender difference at different ages, which is interesting.

I have only a few suggestions for possible improvement:

- It would increase the readability of the paper when a figure would be added in which all (possible) underlying mechanisms are displayed.
- There is a suggestion that there may exist a gender difference in the effectiveness of primary prevention measures of respiratory symptoms (Schonberger et al. ERJ 2005;25:660-70)⁴. What could be the explanation?

⁴ The author would like to comment that, though she is convinced of sex differences she did not deliberate on the suggestion that there may exist a gender difference in the effectiveness of primary prevention measures of respiratory symptoms, because of lack of evidence.

Discussion

What is the state of the art as regards integration of attention to sex and gender issues in the methodologies of basic and clinical research?

Suggestions were made to study the interaction between genetic disposition, sex and environmental influences in the development of asthma. This paper focuses on biological differences; gender aspects are missing. This is largely due to the fact that there is hardly any literature on this topic in asthma available. Results from different studies conducted on asthma within different disciplines should be combined.

Sex seems to be a confounder; suggested is stratification between males and females.

Again the question emerged what the number of participants needed in each study would be, if stratification between the sexes is applied. Not all participants agree on having to use an excessive number of participants in studies about gender aspects. "Size of the study is not important if the recruitment is selective, based on gender".

According to the participants, more attention should be given to certain biases that influence the results of these studies about sex differences in asthma. The results are marked by gender-related issues. Women and men have different clinical symptoms. Furthermore parental reporting about symptoms of asthma differs between their sons and daughters. In addition, in recruiting research participants, the researchers should be aware of these issues.

What are sex and gender differences within asthma and what are the consequences for diagnostic, preventive and therapeutic interventions?

The author started her presentation on sex and gender differences with her observations: "I observed that asthma is more severe in women than in men". However asthma is less prevalent in girls than in boys. "Male:female ratios change over time, the prevalence differs between the sexes as well as number of deaths". Asthma is more prevalent among young boys than young girls (ratio is 2.1). In adults the ratio decreases to almost one. In adult women asthma becomes more prevalent, due to airway and lung growth, hormonal changes, airway hyperresponsiveness, immune development. In females asthma is more severe, there is higher mortality and women have more and longer hospitalisations.

Though the author does recognize that these differences might be due to under-diagnosis by the physicians, she focuses on biological differences between the sexes.

Perhaps the difference in prevalence among young children can be explained by the Yentl effect. There is an under-diagnosis in girls, especially in low-income groups.

More boys receive treatment; girls are less likely to be treated. More asthma is reported in boys by their parents. This bias is also apparent in research and questionnaires. Recruitment bias influences clinical data. Furthermore diagnosis by physicians is biased; girls are less diagnosed with asthma despite the same symptoms, and adult women are more rapidly diagnosed with asthma and men with COPD. Asthma and COPD are sex-related labels, which are almost inherent in the mind of the diagnosing physicians, the author agrees.

Besides the diagnostic differences between boys and girls and men and women, the author claims there are certain biological sex differences that are related to the development of asthma. For instance the sex differences in the development of the pulmonary system are visible in utero. The branching of the pulmonary system is dissimilar for males and females, due to sex hormones. Girls have relatively larger airways in proportion to lung volume than boys.

The author questions the interaction with genetic background and hormonal influences and these sex differences; the participants in the discussion miss the more environmental and social aspects of disparity in asthma prevalence, incidence and severity between males and females.

On a social level, there is a distinction between high-risk and low-risk families for the chances of getting asthma, which is evidence of an interaction between genetic disposition and social environment.

The author does not acknowledge why the risk of asthma in high risk children – that is, children with parents with asthma - and low-risk children – children with asthma-free parents - is merely based on social influences. This may also be due to genetic background. Indeed children in high risk families have a higher prevalence of polymorphisms in some genes compared to low risk children, as far as studies currently demonstrate.

Furthermore there seems to be a link between breastfeeding, behaviour and asthma; boys are breastfed for a longer time than girls (especially the case in high-risk families). Varying lengths in breastfeeding could imply variation in exposure to allergens. A possible hypothesis is that boys are breastfed for a longer time than their female siblings, which means they are exposed to allergens from their mother for a longer time. Another hypothesis is that girls would be getting more foreign environmental stimuli because of additional feeding from the bottle.

Other environmental factors, affecting sex differences, present in family context, are for example smoking behaviour of the mother, type of cooking, and house mite reduction strategies.

If the mother smokes, the negative effects on health of the children are greater than if the father smokes. Mothers are the ones who generally stay at home, thus her smoking has more effect on the children's health. A mouse model shows that if the mother smokes, it has more effect on the in utero female foetus. The effort needed to quit smoking, is different for men and women.

Gas cooking increases asthma incidence among females, but females are usually the ones who do the cooking. All of these are clear indications of the interaction between behaviour and biological differences between men and women.

Some authors have investigated the effect of reduction of allergens in females and males separately, and only found a significant effect in females, but no significant effect in males. They did not formally test whether the effects in females and males were statistically significantly different. This study did not investigate whether reduction of allergens actually prevents asthma. The study analysed children up to two years of age. At that age asthma can not be diagnosed in children, because lung function tests cannot be performed on children of that age. Many 2-year old children wheeze, yet do not develop asthma; therefore the author does not totally agree with the above argument.

Some research has been done showing that peer pressure on boys is huge with respect to not use inhalers in public. In adolescence, boys because of peer pressure hide their allergies and asthma and do not use inhalants. Girls on the other hand, incorporate their asthma in social circle. Gender identity and socialisation is important in therapy compliance. Men and women, the sexes, may respond differently to treatments, due to biological, environmental and social influences.

What are the conceptual and theoretical challenges?

Sex and gender in asthma is an "unsolved puzzle". "The prevalence of asthma is increasing in all countries" worldwide. However there are differences between countries.

As the reviewer of this paper states: The focus of this paper is on biology and asthma, on biological differences between the sexes rather than on gender. The interaction between the biological and behavioural factors regarding asthma could have been considered a little further. There is little literature on the topic of asthma and gender, and therefore these factors were not explicitly in the review paper. This topic clearly needs to be explored in research on asthma and asthma development.

Social patterning, social position of the parent, diet, housing quality, gender-related factors all influence asthma symptoms, prevalence, and incidence. Uses of inhalers, parental symptom reporting, diagnosis, and environmental disposition are more related to gender than to sex.

More research needs to be done on interaction between gender and behavioural change. How does gender affect behaviour change? Behaviour and gender, the interaction, contributes to asthma, but the question is how.

For instance, stress is relevant in modulating hormones. Stress, especially cumulative life-time stress causes higher levels of cortisol. "It is very important to study the relationship between sex hormones (oestrogen, progesterone and testosterone) and the immune system".

What are the ethical and financial difficulties concerning integration of sex and gender in biomedical and health related research?

"Pharmaceutical companies do not set out to study differences between males and females because it might affect incomes". Pharmaceutical companies are not interested in paying for stratified research. Generally speaking there is a lack of the gender perspective and lack of funding and financing of research into sex and gender differences. If drugs are shown to be effective in the total population, drugs can be sold to the total population, but if drug is only effective in specific populations, potential purchasers are excluded. The participants of the meeting find the reluctance of pharmaceutical financing nonsensical.

However in funding, the pharmaceutical industry has a large impact on how research is done. It is important to address this barrier. To obtain grants for research on gender issues is difficult, but not only the pharmaceutical industry is reluctant. It is hard to get grants for gender-focussed research. A possible solution is a strategic approach in balancing funder demands and scientific interest (i.e. Not naming stratification on your application for funding, but in the end stratifying anyway, or "fiddle" sex and gender into proposal).

It seems that the EU would like to focus on gender issues. Question is how to proceed? Researchers state it is relatively easy to incorporate hormonal cycles in research designs, if granted with the financial support. But many funders do not think it is relevant to study sex differences. Awareness raising is a start. Often people are consultants for pharmaceutical companies or for EU. They may not speak up because of their own financial situation. We need to combine our strengths, our scientists, to address the pharmaceutical industry.

In comparison, the pharmacological industry IS interested in sex differences in osteoporosis, because osteoporosis is more prevalent among women. Then again they're not interested in men. However, if you treat both sexes separately, we will need separate proofs.

The participants more or less agree on the necessity of stratification between the sexes, especially in medicine related research. Certain medications might have different (side) effects in men or women. Therefore they should be studied separately in men and women. Many believe that there should be an obligation to stratify between the sexes, before registration of drugs.

A contradiction between the European policy on gender equality in health research and the Research Ethic code is mentioned. The European policy on gender equality in health research is not reflected in the EU directive on clinical research. The directive does not include recommendations on how to enhance gender equality or stratification or participation of male or female animals or subjects. Research proposals should require inclusion of women.

What are the implications for research and policy recommendations?

Recurring themes are funding/financing of research and incorporating the gender perspective in pharmaceutical and EU grant proposals. Generally speaking there is a lack of the gender perspective and lack of funding and financing of gender differences!

It is generally acknowledged that sex differences should be introduced in research. Until now researchers find that if gender/sex differences is incorporated in the proposal, chances for receiving grants are limited. Social (and gender) patterns in asthma are not considered, not by the industry, but also not by researchers. It should be encouraged to focus on sex differences, its underlying mechanisms and social implications.

Summary of main discussion points

- Resistance of pharmacological industry concerning sex difference studies.
If drugs are shown to be effective in the total general population, drugs can be sold to the total population, but if drug is only effective in specific populations, potential purchasers are excluded.
- E.g. Pharmacological industry IS interested in sex differences in osteoporosis.
- Acknowledgements that sex differences should be introduced in research, however if in a proposal the focus is on gender/sex differences chances to get the proposal financially accepted are limited. Focus on sex differences equals no money.
- Social (and gender) pattern in asthma not considered, not by the industry, but also not by researchers. This should be encouraged.
- Contradiction: the Research Ethics Code does not demand sex stratification, this is in conflict with the EU gender equality policy for research.
- Possible solution is a strategic approach in balancing funder demands and scientific interest (i.e. Not naming stratification on your application for funding, but in the end stratifying anyway).
- Different parental reporting: more asthma reported regarding boys.
- Use of inhalators among adolescents: boys hide from peers, girls incorporate asthma in social group.
- Link between breastfeeding, behaviour and asthma: boys are breastfed for a longer time than girls.
- Issues of recruitment.

Paper 3

Methodological ramifications of paying attention to sex and gender differences in clinical research.

Abstract

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Essential in studies on differences in effect based on sex is the evaluation of effect or accuracy estimate differences between patient groups based on sex, i.e. the analysis of effect modification. The use of absolute risk differences to illustrate differences in treatment effect size between sexes should be preferred to facilitate decisions on diagnostic and /or treatment strategies separately for sexes. Confounding can be introduced by an unequal distribution of potential effect modifiers of prognostic variables associated with sex or gender. Therefore, differences in the distribution of presumed effect modifiers or prognostic variables should be presented and, if possible, taken into account. The choice of a statistical model for analysis should be based on the effect measure that was chosen to measure treatment effect. If risk ratios were used, analyses should be based on a multiplicative model. In addition, due to a possible association between sex, gender and prognosis, interactions between treatment and sex should be analysed by calculating the effect of treatment within each of the sexes and subsequently comparing these effect sizes with each other. For the use of results in meta-analyses, point estimates and their 95% confidence intervals should be presented for each sex separately.

Comments

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Abstract

Sex is an individual level variable that should be part of all research analyses. Sex-disaggregation of data must be done with rigor and caution not to commit epidemiological errors. Disaggregating research data by sex may be a prerequisite for but, in itself, is not sufficient to claim that gender has been included in clinical research. Gender can be the lens through which research results are interpreted but, again, this does not insert gender into the research, itself. Gender is somewhat like social capital. It describes a set of social conditions that operate across a group. Unlike social capital, at present, it is unlikely to appear as an independent variable whose effect on the study outcome is assessed. Perhaps the time has come to develop a "gender index", a summative variable composed of a number of group level measures of gender equity. Such a variable could be used in multi-level analyses and in individual level studies to assess the role of gender in health outcomes.

Introduction: sex differences

Men and women are more alike, genetically and biologically, than they are different. Given the fact that both sexes share about 99% of their genetic material phenotypic sex differences are quite remarkable. The failure to disaggregate research data on the basis of sex, and the willingness of researchers to generalize from male research subjects to female populations could reflect the belief that differences within each sex (e.g. amongst men) are greater than differences between or across sexes (within group variation versus between group variation). On the other hand, not reporting research data by sex may be a manifestation of bias, that is, of assuming that study data gathered on men (for example) are generalizable to women. And so, characteristics such as age, income, blood pressure, etc, are documented and become units of analysis while sex does not. The difficult question is when do between group differences (with the groups being men and women) matter enough to validate using scarce resources to identify them (remember that researchers often cite the cost of large studies as a reason for excluding women). And, of course, none of those between group differences will ever be found if they are not sought.

Defining clinical research

A working definition of clinical research may be useful prior to commenting on the paper by Prins et al. (accessed Jan. 8, 2007), the NIH Director's Panel on Clinical Research Report to the Advisory Committee to the NIH Director, December 1997.

Definition of clinical research:

- (a) Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. This area of research includes:
 - Mechanisms of human disease
 - Therapeutic interventions
 - Clinical trials
 - Development of new technologies
- (b) Epidemiological and behavioural studies
- (c) Outcomes research and health services research.

Sub-analysis by sex in RCTs

In general the authors have limited their paper to describing valid identification of sex differences in research and have stated that gender is a useful concept in interpretation of research rather than in research design. They explain some of the errors researchers can make in the design and analysis of RCTs (as the example of clinical studies) and illustrate the nature of those errors using sex as an example. To expand upon one such illustration: Prins et al explain that if treatment and control groups in an RCT are subdivided by sex to look at outcomes, this subdivision is not random and so, the benefit of randomisation (that it distributes unidentified variables equally between the 2 groups) is lost. The importance of this, according to the authors, is that sex may be a confounder or a proxy for some other variable in the causal pathway between treatment and outcome. In other words, one cannot assume that because the women in an RCT have better outcomes than the men in that study, that the treatment is more effective in women. There may be some trait that is more common amongst the women in the study (than amongst the men) that is related to sex but is primarily responsible for the association observed.

Assuming “within group” homogeneity

One of the hazards of the above approach, not explored by Prins, is the assumption that there is homogeneity within the group “men” or the group “women” and that all women can be analysed as a unit. There are, however, a number of within group variables that have been shown to influence numerous clinical outcomes but are rarely identified in clinical trials. It is possible that no association may be found between a treatment and an outcome amongst women because timing of menstrual cycle was not considered. So, for example, if female subjects are at different points in the menstrual cycle at the time of the intervention being studied this may skew findings. A positive outcome early in the cycle and a negative outcome later in the cycle would cancel each other out, making it appear that the treatment had no effect in women. (Menstrual cycle would be an effect modifier in this case – I think).

Gender: a hidden variable in clinical research

If gender cannot be captured in clinical research but only in the interpretation of results of that research then this suggests either that social factors do not influence clinical outcomes (and therefore need not be measured) or that these social factors can be essentially eliminated from the analysis by randomisation (which then distributes these factors equally between groups and makes them unimportant as independent variables). The strength of randomisation is that all those unmeasured factors will be equally distributed across groups and can, therefore, be ignored without being identified. This eliminates them from being considered as related to, or causative agents of, the outcome being measured. There is a body of literature that criticizes how social factors are made invisible rather than treated as independent variables in RCTs. Income is frequently such a factor. When, however, the association between income and health outcome is examined rather than being controlled for, income is often the strongest correlate of health. If it is ignored through randomisation confounding associations will be identified but the central role of income will disappear. Is this true for gender? Because we have not identified a variable that is a marker for gender (particularly for gender as a variable in multi-level analyses) are we blinded to its effect on individual level outcomes?

In summary, then, the major shortcoming of clinical trials with respect to gender is that they control for, rather than identify the contribution of this social determinant to the measured outcome.

Collecting information about gender effects

In gathering background data about study experiments we often consider as important – age, co-morbidities, smoking history, drug use. I wonder how often background data collected includes a history of physical or sexual abuse, measures of control at home and in the workplace, etc. Yet there is strong evidence that these factors (elements of gender) are highly correlated with health and illness. These are the sorts of measures that could be combined to create an index of gender equity.

Gender bias in variables measured in clinical research

Researchers should consider whether the variables that are measured in clinical research reinforce gender biases. For example, does the Gini coefficient (of income inequality) or any measure using household income assume that a woman's relationship to household income is the same as a man's within the same household? Does self-reported health result in minimizing of men's illness status and magnifying of women's because of roles that encourage men not to complain and to be tough?

Measuring the effect of gender

Most existing literature on the importance of gender in epidemiology highlights the need to interpret findings through a gender lens, that is, to be aware of gender as an explanatory factor for findings. However few, if any, attempt to describe gender as an independent variable for use in, for example, a regression analysis. There are no composite indicators of gender equality comparable to the measures epidemiologists have developed for social capital. Is this because the concept of gender as an epidemiological unit of analysis is not valid or because no one has thought of it?

What follows is a non-epidemiologist's ideas about how gender can be inserted into research analyses. Gender has a contextual level effect. It is a variable defined at a "higher" level or a group level that may then affect a lower level (or individual) outcome. It is, potentially, a derived group level variable. For example – gender may have a contextual effect on disease or incidence rates such as HIV, teen pregnancy, and survival after a heart attack, etc. This would be referred to as a cross level effect (or an ecological effect?) meaning a group level variable such as gender exerts an effect on individual level outcomes such as health, disease, risk, etc. This cross level effect would be similar to that of income inequality or social capital.

Gender could be a mathematically derived variable (a summative variable) – collapsing a group of measures of gender equity such as ratios of women to men having higher education, income of women as a percentage of that of men into a "gender index variable". Some of the group measures will have no individual level equivalent (in which case the group level variable is more appropriately named an integral variable) while others may (the summative term is then a derived variable).

What is the appropriate group or unit across which one measures a contextual effect such as gender? In defining a derived group variable like gender, one must define the group. Is this based on geography – that is, neighbourhood, state, country, on religion, on income, or on some other grouping? Behind this question is a recognition that the effect of gender will vary with income, education, and other social factors. In epidemiological terms this is a way of identifying the cross level interaction between gender and variables such as income, religion, race, etc with individual health.

To summarize my thoughts on sex and gender in clinical research – sex is an individual level variable that should be part of all research analyses. Sex-disaggregation must be done with rigor and caution not to commit epidemiological errors. Disaggregating research data by sex may be a prerequisite for but, in itself, is not sufficient to claim that gender has been included in clinical research. Gender can be the lens through which research results are interpreted but, again, this does not insert gender into the research, itself. Gender is somewhat like social capital. It describes a set of social conditions that operate across a group. Unlike social capital, at present, it is unlikely to appear as an independent variable whose effect on the study outcome is assessed. I would propose that we need to create a "gender index", a summative variable composed of a number of group level measures of gender equity. Such a variable could be used in multi-level analyses and, perhaps in individual level studies to assess the role of gender in health outcomes.

Discussion

What is the state of the art as regards integration of attention to sex and gender issues in the methodologies of clinical research?

This paper focuses on the methodological point of view in sex and gender research.

Sex is considered a binary variable. Sex is a variable is associated with therapeutic efficacy, diagnostic accuracy, and etiological impact. Only association, not cause and effect can be proven. Often the effects of sex on the outcome measures are relative, due to interaction and effect modification. Sex operates on the individual level.

Randomized controlled trials, which are standard in clinical research, make it impossible to use sex as a variable because sex cannot be randomized. Stratification is the only option and then cohort comparison ,should be conducted. Problem is the sample size and the money needed for larger samples. Without randomization you always encounter statistical power problems. To combat power issues in conducting

subgroups studies, researchers should do power calculations beforehand. Baseline risk measurements show differences between male and females, which also could imply that varying numbers of participants per subgroup are needed. These baseline differences can be used in power calculations in relative risk reduction analysis.

Suggested was, instead of stratification, recruiting males and females and then randomize them to the different experimental groups. Sex disaggregated research would be a good design and multilevel analyses a good statistical method.

Further there is a heterogenic effect within the subgroups of men and women. In sex research one of the pitfalls is the assumption of homogeneity of sexes. What about the menstrual cycle: is that an effect modifier? Sex however interacts with other variables. Interaction is hard to deal with, the more interaction between variables and sex/gender, the N has to more than double. Problem of sample size: Not only 2:1 ratio female: male rats, but taking the oestrogen levels into account at least 4:1 ratio. With more interaction (meaning co-variation) the ratio will exponentially large (e.g. $4 \times 2:1 \times 2 = 8:2$ or $4 \times 4:1 \times 4 = 38:4$).

Sex operates on the individual level. There are sex differences between diseases and interactions of disease and sex. Even the placebo effect is sex dependent. It seems that the only solution would be to test the populations (men and women) separately! This means we need to conduct two studies instead of one.

Gender factors are even more difficult to deal with; gender as an explanatory, independent variable. The reviewer deliberates on the possibility of creating a gender index, comparable to the Gini coefficient. A gender index seems a good alternative; but what variables should be included in such an index? Each disease probably has certain salient gender aspects which are of influence, therefore the gender index will vary per disease.

What are the conceptual and theoretical challenges?

Systematic reviews show no standard reporting of sex and gender differences. Perhaps the limited number of words allowed in biomedical articles, papers, and proposals, could lead to dismissal of sex and gender aspects.

The idea is to somehow unravel or “unpack” gender: Where to start? The discussion was a conceptual discussion about how sex and gender and the relationship between variables could be perceived and measured. The author seems to mainly refer to sex, and how to incorporate sex into sex-difference studies. The commentator tries to incorporate the notion of gender, which is much more difficult to measure statistically.

Which practical tools do researchers need to ensure a better integration of sex and gender aspects in clinical research?

The tool that the reviewer mentions is a gender-index, which should be used in statistical designs. After discussing this option no consensus is reached. The United Nations Development Program (UNDP) suggested introducing a gender-equity-index as a confounder to correct for gender. In practice, using these indexes is very complicated, because there is no straightforward answer to which other variables should be included.

What are the ethical and financial difficulties concerning integration of sex and gender in clinical research?

Sample size will need to be increased in the suggested research designs. More money is needed for larger samples. “Money is tied to the overall effects”. With more interaction (meaning co-variation) the ratio and the costs would increase exponentially.

In conducting separate studies for men and women, the N in both trials should be equal. It is difficult to recruit a sample size of women. For instance, several researchers have trouble recruiting the same number of women and men in clinical trials; usually only 30% of the sample is female.

What are the implications for research and policy recommendations?

Regulatory documents should be written to regulate sex and gender research! Perhaps we should try to create a gender index. But then we also need a compilation of other factors related to health: educational, political factors etc. which should be included in the gender-index. There is so much data; instead of gathering more data, we should re-analyse the data on sex differences with a gender perspective using other analytical methods.

We should aim for equity and not equality! This means that we should look at differences between the sexes, but give them the same priority. For instance, taking osteoporosis as an example, osteoporosis medication is tested primarily in women, but is also prescribed to men. A separate trial should be conducted in men. Clinical research should be focused on the individual level, because of the heterogeneity within each sex.

General comments to be taken into account: gender is a global effect, heterogeneity within sex.

Summary of main discussion points

- Conceptual discussion about how relationship between variables is perceived, measured.
- The placebo effect is different for the sexes.
- Problem of sample size: Not only 2 female rats: 1 male rat ratio, but taking the oestrogen levels into account the ration becomes at least 4:1. With more interaction (meaning co-variation) the ratio will exponentially large. The costs would increase exponentially.
- Furthermore it is difficult to recruit this sample size of women. Some researchers, for instance, have trouble recruiting the same number of women and men in clinical trials, usually only 30% of the sample.
- Methodological problems: gender cannot be measured.
- Idea is to somehow unravel or “unpack” gender: Where to start?
- United Nations Development Program (UNDP) suggested introducing a gender-equity-index.
- Can this index be used as a confounder to correct for gender? Very complicated, what other variables will you want to add?
- Osteoporosis: drugs tested in primarily women, and they are prescribed to men.
- Final remark: test populations separately! Two studies instead of one, because randomisation on sex is not possible.

Paper 4

Integrating a gender dimension in osteoporosis and fracture risk research.

Abstract

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Sex (referring to its strict biological sense) and gender (referring to the socio-cultural dimension) are major determinants of health and disease. The aim of this review is to examine differences between sexes in the prevalence of osteoporosis and fractures and their risks in terms of bone- and fall-related factors and to review differences between genders in relation to the perception of fracture risk and the possibilities of prevention of fractures.

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The incidence of fractures differs between women and men: it is higher in boys than in girls and the burden of fractures in adults increases with age, and is higher in adult women than in adult men. With life expectancy growing the yearly number of fractures is likely to increase substantially. Vertebral, hip and other non-vertebral fractures in adults result in increased mortality (more in men than in women), increased morbidity (equal in women and men) and high costs (more in women than in men).

The reasons for the differences in incidences of fractures between men and women are multiple. They are related to the many factors that determine fracture risk: those related to bone and those related to falls. Such differences, but also similarities, have been documented from the molecular and cellular level up to the organ level. Sex hormones play a central and essential role in the physiology of bone. Sex hormones have a wide array of functions and influences on bone, cartilage and muscle cells by direct and indirect mechanisms. Differences in sex hormones therefore directly and indirectly contribute to sex differences in fracture risk.

Adult men fracture less because they build up structurally stronger bones than women and which they are able to maintain longer. Men build up larger bones during growth with better micro architecture and thereafter have less increase in bone remodelling. Furthermore, they develop later bone loss and fewer older men are hypogonadic than women.

Case finding strategies for patients at risk for fracture, including bone densitometry, is much better documented at the population level in women than in men.

Drug therapies that reduce the risk of a broad spectrum of fractures, even within short term, are more clearly demonstrated in randomised controlled studies in women than in men. Drug therapy is more widely available for women with osteoporosis, but only scarcely for men with osteoporosis.

In how far perception of osteoporosis could be different between genders is less well documented. In general, osteoporosis is under diagnosed and under treated both in women and men, and related to limits in patient's and doctor's awareness at all clinical stages, from case finding to compliance and persistence of therapy.

Comments

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The paper by Geusens & Dinant is well constructed and has a logical framework to analysing the factors that affect the development of osteoporosis and its impact from a sex and gender perspective. Many important issues are identified, with numerous charts and graphs giving a lot of detail, however this mass of description could have benefited from more discussion of the issues, but this may have been a constraint imposed by word limits. Nevertheless the balance was skewed towards the biological sex based differences and away from the gendered nature of the disease and how society frames both the risk of acquiring this disease and its impact on the individual, the health services and the population. The authors are right in recognising that generally this is an under researched area and that future research should be cognizant of sex and gender as important factors.

There are a few areas that could have been considered within the review and these are outlined below:

1. An addition to the report could have been a discussion of the gendered nature of the main secondary causes of osteoporosis in men: the use of glucocorticosteroids, hypogonadism and chronic alcohol use.

The influence of glucocorticosteroids on bone density through the treatment of injuries or conditions such as COAD is an instance where a more gender specific problem exists, due to the larger number of men affected (Vestergaard et al 2005).

Hypogonadism – the role of the androgen deficiency in bone deposition is well documented (Zitzmann & Nieschlag 2004, Lim & Fitzpatrick 2004) and the controversy over its role in bone loss has been covered within the review, though this could have been expanded on further.

Alcohol abuse is still seen to be a mainly male phenomenon, and its importance with the implications on bone loss is underreported and could have been highlighted as an area in need of further research and health promotion activity. The role of smoking as a cause of bone loss is particularly important in men, though the number of young women now smoking should also be considered a warning of increased risk for them as well.

2. It would have been useful to have had an expansion of the discussion relating to men's increased number of 'co-morbidities' as mentioned in the section on 'mortality after fractures'. As well as the issue raised above in relation to the use of steroids for lung disease there are also the emerging literature on the specific problems men are facing through the treatment of prostate cancer, which for many men involves androgen ablation therapy and its effect on oestrogen levels in men (Lee et al 2005) and it appears that men who have had a myocardial infarction are also at risk of developing the disease, though this may be as a result of related lifestyle issues such as inactivity, smoking and diet (Magnus & Broussard 2005).

3. An aspect that has occurred elsewhere i.e. with coronary heart disease, is that neither the sufferer nor the health professional see the possibility of the illness within that gender (or age group, for younger women at risk of osteoporosis) and therefore the problem goes undetected for longer. This notion of candidacy (Davison et al 1991) is one that could have been developed further within the paper.

4. The importance of bone deposition within the younger generations and the impact this has in later life is also a factor that was worth considering. Maximum bone density has to be attained by the age of 40 years and this is influenced both by sex and gender. In the young the age of puberty is known to occur earlier in women than in men such that the rate of bone deposition is higher in females, who reach peak bone mass faster than males. However in girls who are undertaking extreme exercise and have a poor diet this is disrupted by exercise-associated ovarian suppression and amenorrhoea (Bennell et al 1996). Bone deposition and bone health is also affected in males who experience premature bone loss as a result of regular and prolonged exercise coupled with poor diet (Stewart & Hammond 2000). The role of androgens in affecting bone strength is also worthy of further research and debate (Seeman et al 2006).

Young men's increased bone density was also partly explained by the extent of their participation manual labour. However current demographic trends are suggesting that men are now more likely to be in similar jobs to women and have been found to be living more sedentary lives, which will decrease the rate of bone deposition and further add to the burden of the disease in later life.

5. It was noted that more men die following fractures than women, despite their numerically smaller numbers. In the review this was noted as an issue of co-morbidity, but there is a further issue gaining prominence and that is in relation to the relative lack of social support in older men who live alone and the implication this has for recovery following fractures. Women tend to have better developed networks of friends that help out in times of difficulty, these same resources tend to be lacking in men, leaving them without support systems built on friendship and this has an implication for both the physical recovery process but also on the emotional labour of recovery and rehabilitation (Davidson et al 2003).
6. With women having increased screening opportunities there is also the issue of women coming more frequently into contact with health professionals who can pick up emerging problems at an earlier stage (White & Banks 2004). The issue of health literature and indeed general health messages being more focused onto women also ties in with the reduced awareness of men to the problem of bone health.

In conclusion the review gives a good description of the sex related differences between men and women and rightly highlights the need for more specific research onto the issue of sex and gender for osteoporosis. The paper also opens up a debate as to what factors are relevant when considering bone health in the population and its urgency when projections for problems for both men and women are considered.

Discussion

What is the state of the art as regards integration of attention to sex and gender issues in the methodologies of clinical research?

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We need more and new data on the effects of diet, sun, and sports for men and women. Perhaps different outcome parameters and proxy outcomes, for men and women, have to be applied. Separate trials in men and women need to be carried out. Also more fracture studies need to be conducted to be sure which determinants are most important. Heterogeneity of the sexes should be considered.

What are sex and gender differences within osteoporosis and what are the consequences for diagnostic, preventive and therapeutic interventions?

Osteoporosis is characterized by decreased bone density, disturbed microarchitecture and defective bone material. Osteoporosis and the underlying mechanisms are different between the sexes, which calls for different outcome parameters. List of risk factors is different for the sexes.

Osteoporosis is generally presented as a female problem and particularly prevalent among postmenopausal women, probably due to changes the oestrogen levels. It seems that bone remodelling is much faster in postmenopausal women, creating brittle bone structure.

There are numerous sex differences concerning the skeleton which are of influence in osteoporosis. Women generally have smaller bones than men, especially the vertebral bones. Load capacity of the bones is higher in male bones. Looking at sex-specific and age-related evolution of bone mass; men build up more bone mass and their bone mass starts decreasing after a longer time compared to women. In men bone loss is related to andropause, and bone loss is moderate. However men have lower life expectancy than women. Perhaps with a longer life expectancy they would have the same bone loss as women. Furthermore there are differences in bone geometry, of cortical bone, and differences in trabecular bone architecture between men and women.

Osteoporosis increases the risks of bone fractures. The annual incidence of hip fractures is much higher among women, especially older women. And the risk of fractures among patients with osteoporosis is much higher among female patients.

The discussion on this paper focused on the consequences of these sex differences and environmental explanations of these sex-differences.

For one, falls are sex-dependent; the female:male ratio is 1.5. This is relative to muscle strength. Boys have more fractures than girls; partly because of the activity level of boys. Boys are more active; engage more in active sports, therefore they fall more than girls. But this difference could also be associated with physiological bone differences. Because of the rapid growth of their bone tissue, the boys' bones are weaker and break more easily than girls'. Perhaps the milk consumption differs between boys and girls, and men and women, which could be another explanation.

The incidence of fractures increases much more among elderly women. One explanation is that falling incidents are high among the elderly, especially among elderly women. This could be because of the effects of oestrogen level on muscle tissue. In the elderly, sex-differences in muscle mass and muscle control are of influence. Women fall 50% more often than men; they have less muscle control and less muscle strength. Cause of falls cannot only be explained by different levels of activity, but also by muscle control, which is lower in women. There are biological and behavioural explanations for sex-differences. The author in the paper focuses more on the biological explanations of the epidemiological differences.

The reviewer of the paper tried to look at the life-style factors of osteoporosis, especially from the men's point of view. Lack of screening among men, reduces the visibility within the health services. It seems that hereditary factors are especially influential in men. Reduction in manual work affects the build up of reserves of bone density in men. There is more co-morbidity in men.

Medication, labelling, dosage, prescription is based on female standards. Whether pharmacological treatment has an effect is sex dependent: A smaller effect among women could be the result because of the lower prescribed dosage due to the side effects. Men generally take more prescribed drugs for osteoporosis.

Over-exercise and dietary restrictions are detrimental for women and men. Running marathons is unhealthy, especially for men. General practitioners (GP) should be aware. Half of the GP's do not recognize osteoporosis. All physicians know how to measure blood pressure; however, they never measure bone conditions. Screening procedures and scans need to be conducted. One of the main determinants of osteoporosis is menopause. If an elderly woman fractures, the GP immediately thinks osteoporosis. Prevention is mainly secondary or tertiary prevention. If the GPs are more aware of osteoporosis in pre-menopausal women and among men, perhaps primary prevention could be successfully applied.

What are the conceptual and theoretical challenges?

The paper considers the biological factors; however it is difficult to find the gender perspective. There is a need for 'gendered' research taking into account co-morbidity, life-style factors and social support from gender perspective. Diet, sunlight exposure and practicing sports are contributing factors to prevent osteoporosis or lower the impact of osteoporosis. Also lifestyle factors like alcohol use and smoking, and social factors like social isolation and social networks are gender related.

Social change increases the incidence and prevalence of osteoporosis. Osteoporosis is under treated in women and men. The instructions for use of medication are directed at women, and therefore gendered.

Osteoporosis is a typical women's problem, hence research is conducted among women. The case of osteoporosis is a clear example of candidacy, that is: it is not visible among men, thus research and medication focuses primarily on women. Lack of screening among men reduces visibility. Awareness of this candidacy is low with doctors, patients, men and women.

Women are the focus of research in osteoporosis, and serve as standard (also for men). There is hardly any research done among men. Sex related mechanisms differ in physiology of the diseases; perhaps in all diseases. We may need different outcome parameters for men and women.

Not only is the disease stereotyped, but also gender stereotyping with respect to falling needs to be examined. Mobility patterns for men and women are different.

"Gender equity in misery": women and men each have their own problems in health and disease.

Expert

What are the ethical and financial difficulties concerning integration of sex and gender in biomedical and health related research?

Meeting

Hip fractures are most important and costly. The World Health Organization states: Focus on high risk population which is in this case based on age (elderly) and gender sex (women), this should be extended to other at-risk populations.

GenderBasic.

Promoting

integration of

What are the implications for research and policy recommendations?

There are many people and patients at risk; both men and women. These people at risk need to be identified. More trials are needed, also on the side effects of medication, as well as new screening procedures and scans. Labelling should be sex-free. Perhaps the Osteoporosis Foundation will be helpful in granting finances.

sex and gender

in biomedical

and health

related research

Summary of main discussion points

- Cause of falls cannot only be explained by different levels of activity (i.e. Gender roles), but also muscle control, which is lower in women (biological explanation).
- Women are the focus of research in osteoporosis, and serve as standard (also for men).
- For men: running a marathon is unhealthy and bad advice.
- Importance of screening.
- List of risk factors are different for the sexes.
- Whether pharmacological treatment has an effect is gender dependent: A smaller effect among women could be because of the lower prescribed dosage due to the side effects. Men generally take more drugs.
- There is “Gender equity in misery” (women and men each have their own problem).

Paper 5

Sexually dimorphic gene expression in somatic tissues.

Abstract

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The sexually dimorphic differentiation of the bipotential gonad into testis or ovary initiates the sexually dimorphic development of mammals and leads to divergent hormone levels between sexes for the entire lifetime. However, despite the fact that anatomical and hormonal differences between genders are well described, only a few studies investigated the manifestation of these differences at the transcriptional level in somatic tissues. More recently, the application of microarray technology enabled the systematic evaluation of sex-biased gene expression on transcriptome level indicating that the regulatory pathways underlying sexual differentiation are giving rise to extensive differences in gene expression in adults. A sustainable annotation of sex-biased gene expression represents a key towards the understanding of basic physiological differences between males and females in the healthy as well as diseased condition. This review focuses on basic regulatory mechanisms of sex-specific gene expression and discusses recent gene expression profiling studies to outline basic differences between sexes on transcriptome level in somatic tissues.

Comments

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The paper "Sexual dimorphic gene expression in somatic tissue" by J. Isensee and P. Ruiz Noppinger gives a clear and elegant presentation of the current knowledge on sex dependent differential gene expression in somatic tissue (i.e. tissues other than the sex organs).

While the initial stages in embryogenesis are identical between male and female fetuses, differentiation into the two sexes starts to occur during gestation (day 10.5 in the mouse, i.e. after approximately half of the intra-uterine period). If a Y chromosome is not present, the foetus develops into a female. The SRY (Sex determining region of the Y chromosome) induces the male sex in the foetus. SRY acts by inducing production of the transcription factor Sox9 that induces a gene program leading to testosterone production and differentiation of the previously bifunctional gonad into a testis, instead of an ovary, which would otherwise be its destiny.

Interestingly, different groups of animals employ widely different strategies for producing the two sexes necessary for sexual reproduction. Birds have Z or W chromosomes and turtles develop into males or females depending on the temperature prevailing during egg hatching. One mammal has lost its Y chromosome (the mole vole, *Ellobius lutescens*), but can still produce males and females. Despite this, upregulation of Sox9 leading to reprogramming from the female to the male differentiation pattern in the gonad appears to be the common mechanism for sex differentiation in all vertebrates.

X and Y chromosomes

Women have two X chromosomes, men have only one. The X chromosome encodes approximately one thousand genes, or 4% of the total number of genes. To avoid that women produce twice as much protein from all these genes, one of the X chromosomes is inactivated in the cell, this inactivation randomly affects one or the other of the X chromosomes. However, some of the genes encoded on the X chromosome escape inactivation and, to compensate for this, the single male X chromosome is transcribed at the double rate.

So far, 27 genes have been identified on the human Y chromosome that make proteins unique for the Y chromosome.

Sexual dimorphism in the gonads

The reproductive tissues are the organs that show the greatest sex differences. Several hundred gene transcripts from the gonads show at least a 3-fold difference in expression between males and females. Sexually dimorphic genes in the gonads are outside the scope of the review by Isensee and Noppinger.

Sex hormones as differentiation factors in non-gonadal tissues

Sex hormones influence gene expression and may be responsible for some differences in differential gene expression in the tissues. Sex hormones act by passing through the cytoplasmic membrane of the target cell, forming a complex with a cytoplasmic receptor that translocates into the nucleus where it binds to various sites on the chromosome and activates transcription. The sex steroid hormone-receptor complex may also interact with other transcription factors present in the nucleus, so called "transcriptional cross talk". Furthermore, sex hormones may also exert effects in the target cell by activating intracellular kinases and thereby intracellular kinase-dependent pathways.

Growth hormone

It appears that much of the sex differentiation seen in somatic tissue is mediated via a difference in growth hormone pattern of excretion from the pituitary gland. In females, GH is excreted into the blood stream in small and frequent pulses, leading to a fairly stable level of GH in the blood plasma. This pattern of production depends on the production of oestrogen and is mediated via the oestrogen alpha receptor ER α . In the absence of oestrogen or the oestrogen receptor alpha, a male pattern of GH is produced. The male pattern consists of fewer and much larger pulses of GH excretion, i.e. a highly pulsatile release pattern creating strikingly varied plasma levels.

The different patterns of GH release have been shown to influence expression of several of the differentially regulated genes.

Measurement of differential gene expression in the sexes

Measurement of differential activity in genes between males and females is done using microarray, and the paper describes the studies performed so far using this technique. In microarray, a large number of probes (thousands to ten thousands) are immobilised on a solid phase. A lysate of the tissue to be investigated is added. mRNA in the cells will bind to the corresponding probe(s) and be quantified. In the reported studies, tissues from male and female rats and mice have been compared regarding content of mRNA for different genes. At least 2-fold or 3-fold more or less mRNA in tissues from one compared to the other sex is usually considered as having a "sexually dimorphic" activation profile.

The paper gives a clear presentation of the relatively few studies so far published that have investigated sex-differentiated gene expression in non-gonadal tissue. The best-studied tissue is the liver. Other investigated tissues include the kidney, adipose tissue, skeletal muscle and brain.

In general, the kidney, liver and adipose tissue are the non-gonadal tissue that displays the highest degree of sex-differentiated expression. Around one gene in one hundred active genes shows a substantial (>2-fold) difference in expression between the sexes.

In the liver, genes involved in electron transport, among them cytochromes, genes involved in lipid and steroid metabolism are found among the sexually dimorphic genes. Differences in cytochrome expression have bearing on drug metabolism rates, which may differ strikingly between men and women for some classes of drugs. Different expression of genes involved in lipid metabolism may underlie the less atherogenic lipid profile in blood of females, compared to males.

In the kidney, genes encoding cytochromes are differentially expressed between male and females. For example, a major glucocorticoid transporter, Cbg (corticoid binding protein) is expressed in the proximal tubules of female, but not male, mice. Differentially expressed genes are mostly involved in steroid and bile acid biotransformation and may affect drug metabolism.

Skeletal muscle shows relatively little sexual dimorphism between male and female mice with genes encoding spermine and ornithine metabolism are more strongly expressed in males than females.

The brain shows the lowest proportion of genes that are differentially expressed in male and female mice and rats. Among the few proteins that show a clear sex difference is prolactin, which is more expressed in females than males. Prolactin induces growth and development of the mammary glands and milk production.

The effect of cyclicity

Female sex hormones vary according to the menstrual cycle. It is, thus, plausible that gene expression in somatic tissue could vary accordingly. Although the cyclic expression of genes has been investigated in the uterus (in mice and humans), the effect of cyclic sex hormone production on somatic tissue has not been investigated.

Conclusion

It is quite striking that relatively few genes display differential activity between males and females if a 2-3 fold increased expression is taken as evidence of differential activity. Most genes seem to be equally active in males and females, or display only minor differences in activity. The genes that show different activity in males and females often perform functions related to steroid metabolism and, secondary to this, may have profound effects on the metabolism of certain drugs. An important lesson from this is that all drugs must be tested on women as well as men.

Most genes, which are differentially regulated between men and women, are probably involved in reproduction, which is the single reason to have two sexes. Evidently, this reproduction has relatively modest effects on other parts of the body than the reproductive organs designed for this purpose. Interestingly, the construction of two sexes can be achieved in a number of ways. The only thing required is that a program is initiated that changes the initial female differentiation programme into a male one by starting expression of a limited number of genes. The Y chromosome contains little apart from genes performing this functional switch. Practically all other genes originally carried on the Y chromosome have been destroyed.

The lowest degree of sexual differentiation on the protein level is found in the brain. This does, of course, not exclude differences between men and women in how brain cells are connected or in production of non-protein mediators. However, it shows that most of the genes expressed in our brains are neither male nor female, simply human.

Comments

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The concept of sexual dimorphic gene expression is already well established. On a gene-to-gene basis various genes have been identified exhibiting this phenomenon. Recently, the use of DNA microarrays has been introduced by which thousands of genes can be monitored simultaneously at the RNA level for sex-biased transcription. In the present review the authors summarize the recent large-scale searches for dimorphic genes using this novel technology, and intend to concentrate on the underlying basic regulatory mechanisms. They focus on somatic tissues and on rodents, mainly the mouse.

To my overall opinion, the available data are well collected but the authors remain very descriptive even in their final concluding remarks. Although this is not uncommon for the present-day microarray analyses, the review would be more attractive if the authors not only summarize and compare the available data, but in addition try to link them more to the consequences for understanding biological differences between sexes.

Some remarks concerning the applied technology can be made:

First, a technological finding that remains unaddressed is the fact that different technology platforms give a considerably different number of dimorphic genes. The authors state “the platform has a major impact on the detectable sexual dimorphic genes”. This makes it very difficult to determine which platform, if any, represents the genuine *in vivo* situation. A comment would be expected on how to determine the best, or most reliable platform. This is not necessarily the one that gives the most differential genes. In this context it is not mentioned whether in the different studies the results have been confirmed by other techniques like RT-PCR.

Secondly, the authors have used David to identify sex-biased cellular processes in various tissues by gene ontology determination. Additional information might be obtained by running the gene list through a pathway analysis program to try and reveal defined sex-biased molecular pathways.

Surprisingly, a very large number of genes seem subject to sexual dimorphism in the liver but only to a low fold change (1.2 times). This phenomenon seems to be further disregarded by the authors because of their low difference. However, it is nowadays more and more recognized that minor changes of many genes in a single pathway or metabolic route can have significant influence on the biology. Yet another possibility is, that a certain gene is the rate-limiting factor by its level of transcription for a certain pathway. If this gene changes its transcription 1.2 times, a 20% up-regulation of the whole pathway may be important for cell and organism physiology. So to my opinion low fold-change genes may have a large impact.

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Although the authors state to focus on regulatory mechanisms (“this review focuses on basic regulatory mechanisms of sex-specific gene expression”), this topic remains poorly addressed. For instance, one mechanism especially contributing the sexual dimorphic gene expression in the rodent liver is the different production pattern of growth hormone. The consequences of this production pattern are beginning to be understood, but the question then shifts towards the mechanistic origin of sexual dimorphic growth hormone production. The authors do not make this step in their review

More potential mechanisms behind sexual dimorphic gene expression should be mentioned. One mechanism of gene expression regulation is the binding of hormones with their nuclear receptors to the target genes. Further, it has been recognized that post-transcriptional regulatory steps may be involved, but hardly anything more is said about this. Interestingly, the male and female germline cells can modify the expression of so-called imprinted genes with respect to their later expression in the adult individual. Although this is a different aspect related to sex-influenced gene expression, it is tempting to hypothesize that somatic tissues might have a sex-specific adaptation mechanism that similarly involves DNA methylation.

If hormone-directed genes are already active during prenatal development, it would be interesting to discuss the influence of sex on the foetal-programming theory of Barker.

Apparently different tissues do not have a significant overlap of sexual dimorphic genes. It seems to be “highly tissue-specific”. This seems to indicate that there exist tissue-specific sex-organizers, or rather sex-specific tissue-organizers. The authors are requested to comment on this.

It is not indicated how the authors think about the consequences of this type of research for humans. Can sexual dimorphism of gene expression in brain be examined in humans? What would be the meaning of knowing that male and female brain-genes are differently expressed? Could we then better understand sex-dependent behaviour?

Referring to the guiding questions:

1. Does the paper provide a comprehensive state of the art as regards sex and/or gender aspects?
Yes, the microarray studies on sex-biased expression have been comprehensively summarized.
2. Does the paper provide examples of why a focus on sex/gender differences may be relevant for the field of study?
No, comments on the meaning of the outcome of this type of studies for ethics and society is lacking.
3. Does the paper identify what is known, and what is not known?
Yes, but presented knowledge is mostly confined to the technological level.

4. Does the paper suggest relevant questions for further research?

Yes, but only in the field of genomics research.

5. Are there any aspects which may be added from the perspective of the reviewer (e.g., basic research, clinical perspective, theoretical perspective)

Reflections on regulation of sexual dimorphic gene expression are missing; the (future) knowledge has not been put into the clinical or societal perspective.

Discussion

What is the state of the art as regards integration of attention to sex and gender issues in the methodologies of translational research?

“This novel technology is still very immature”. Genomics is a novel research area, but also immature and in development. Results should be verified and validated by other techniques.

“It depends on which of the two used systems is used, which and how many differentially expressed genes you will detect”. Micro arrays make it possible to study 25,000 genes simultaneously.

Variation between animals is not shown. Variation between animals is higher than between sexes.

Studies are done in inbred mice, which are homogenous. Humans are by definition heterogeneous. “We are not inbred. Gender is only functionally relevant in outbred populations”. How can we translate results obtained in mouse models to humans?

What are the conceptual and theoretical challenges?

The review is descriptive, not normative or prescriptive. Research is conducted with inbred mice, creating a homogenous population. Humans (and diseases in humans) are heterogeneous.

Sexual dimorphism: male or female based gene expression; sexual dimorphisms are widespread, but of minor effect. Genomics is studied on a transcriptional level, investigating the whole genome at once instead of single genes, using mice models. Different organs were studied i.e. kidney/liver/hypothalamus and also the human heart tissue. There is species divergence. In the liver, the growth hormone is important in causing differences. Age and oestrous cycles are important. There is a need to link sexual dimorphic gene expression to physical traits.

Are we speaking of “Tissue-specific sex-differences or sex-specific tissue-organs”? What are the social consequences of knowledge of differences between the sexes?

According to this study, sex is in the kidney, liver etc and not so much in the brain. Are we talking about genes or proteins? We need translation/transcription to use these results. The immune system is one of the systems that is the most dimorphic.

What are the ethical and financial difficulties concerning integration of sex and gender in biomedical and health related research?

Genomics is expensive and mainly descriptive. What and where will this lead to?

“We do not know. But we should take the challenge. We should ask ourselves ethical questions, but it should not stop us doing genomics”. We should question the ethical considerations: Continue doing this kind of research to gain more knowledge.

Summary of main discussion points

- What does this research about genes lead to?
- The review is descriptive, not normative or prescriptive.
- Research is conducted with inbred mice, creating a homogenous population. Humans (and diseases in humans) are heterogeneous. How do they correspond?
- Ethical considerations: Continue doing this kind of research to gain more knowledge.
- “Sex is in the kidney”.

Paper 6

The metabolic syndrome - sex and gender related issues.

Abstract⁵

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The combination of the risk factors abdominal obesity, disturbed glucose homeostasis, dyslipidemia and hypertension are believed to represent a distinct entity that leads to a greater increase in cardiovascular risk than the sum of its components and has therefore been defined as an own entity - the metabolic syndrome. In the recent years, the prevalence of the syndrome was greater in men but rose particularly in young women where it is mainly driven by obesity. Diagnostic criteria for the metabolic syndrome vary for the cut-off points and definition of its components in a gender specific manner. Based on the definition of impaired glucose homeostasis, pathological abdominal circumference or waist/ hip ratios, more or less women are included. Glucose and lipid metabolism are directly modulated by oestrogen and testosterone with induction of insulin resistance and a proatherogenic lipid profile by a lack of oestrogen or a relative increase in testosterone. Hypertension is a strong risk factor in both sexes and increases steeper in aging women than in men. Menopause and polycystic ovarian syndromes contribute to the development of metabolic syndrome by the direct effects of sexual hormones. Some components of the metabolic syndrome carry a greater risk for cardiovascular disease in women, such as hypertension and diabetes. Future gender related clinical and research activities should focus on the identification of sex and gender specific criteria for risk management in patients with the metabolic syndrome. We propose small focussed mechanistic studies on sex specific surrogate endpoints and sex-specific studies in animal models for diabetes and aging.

Keywords: metabolic syndrome, menopause, cardiovascular disease, gender differences

Comments

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General comments⁶

The title states “sex and gender related issues” – but the meaning of these words and their possible different importance regarding the metabolic syndrome is not clearly expressed.

Through the paper there is a focus on women whilst the men are more peripherally handled. I lack the balance of a real gender perspective that in my eyes is a more serious approach.

The start is good with discussion of the diagnostic problems and differences in prevalence followed by the different components in the metabolic syndrome (obesity, hyper/dyslipidemia, hypertension, glucose metabolism). Then there is a mix with sex hormones, autonomic dysregulation and inflammation which are not parts of the metabolic syndrome as such.

The treatment part seems disconnected. I think it had been a better idea to integrate this in each part of the metabolic syndrome.

The whole review rattle off fact after fact (sometimes wrong) without a thorough attempt to explain the mechanisms behind the phenomena, which should give a deeper understanding of the metabolic syndrome.

The review is loose in the contour, touches the topic in a very superficial way, repetition occurs, references are missing, and shortenings are not explained. There are no attempts to discuss differences in prevalence in different countries, age, gender and other confounding factors.

For certain there are other diseases correlating with the metabolic syndrome (e.g. renal insufficiency, arthrosis, prostate cancer). The authors do not get any real context as they don't analyze in depth all the facts they give and they don't synthesize the topic to a final decision.

⁵ The abstract included in these proceedings is the latest abstract. The author rewrote her paper making use of the discussions and comments after the expert meeting.

⁶ These comments by Eva Swahn bear reference to the first draft of the paper. Some of the comments may not be relevant anymore as Vera Regitz-Zagrosek rewrote the paper.

It would have been of value to see some current epidemiological curves from different countries and the trends during the last 10-15 years in both genders.

Last paragraph states that genetic variables play a major role in the development of obesity. Is that really so? What is "a male lipid profile"?

There are many articles claiming CRP is a stronger risk factor in men than in women, I lack balance in choosing the references. (See e.g. Garcia-Moll X et al, Eur Heart J 2000; 21:1598-1606)

Comments

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(These comments were not discussed at the meeting)

General comments

This is a well-written paper by an important expert in the field of CVD in women with an outstanding reputation in research on this topic. The scope of the metabolic syndrome is made very clear, with a focus on the causative role of the abdominal visceral fat metabolism in women. The paper outlines important gender differences in abdominal fat metabolism that are closely related to sex hormones. The author reveals an extensive knowledge on the current available gender-specific research of CVD.

Specific comments

Sex-specific differences in CV risk factors are outlined properly and described in detail in several paragraphs. However, the paper does not make any reference to complications in pregnancy that are unique for women and that are important predictors of their future CVD risk. The pathophysiology of preeclampsia for instance shares important similarities with many aspects of the metabolic syndrome and this should be accounted for in risk prediction in women.

The current paper underlines that still many aspects in the pathophysiology of the metabolic syndrome are speculative and not sufficiently investigated yet and I agree with that. As stated in a very recent article on this topic, the role of adiponectin is still controversial in CVD risk prediction, especially in women.

Historically women were excluded from clinical studies either because it was thought that changing levels of hormones through the menstrual cycle would interact with (or modify the effect of) the primary intervention being studied, or because of possible risks an embryo conceived during the study. However, with the inclusion of women in trials, it is odd that data on phase of the menstrual cycle when the study occurs are rarely recorded or included in analysis, despite extensive evidence that treatment effectiveness varies throughout the menstrual cycle.

Discussion

What is the state of the art as regards integration of attention to sex and gender issues in the methodologies of basic and clinical research?

According to the author the Metabolic Syndrome (MetS) is sex-related on several levels.

Features of MetS are insulin resistance, glucose intolerance, abdominal obesity, dyslipidemia and hypertension.

Several measurements can be used in diagnosing MetS. However, there are sex-related differences in the measurements (e.g. in glucose metabolism).

Fasting glucose levels; men always have lower glucose levels than women

Glucose tolerance; men and women are equal: but this measurements is more time consuming to assess

Obesity and insulin resistance; these are significant contributors to MetS in women but not in men

Another measurement was proposed: waist circumference, which can also be taken in men, and hip-waist ratio. MetS is a difficult syndrome to assess: it is composed of many interacting symptoms, biological, genetic dispositions, and life-style factors that also interact.

MetS should be analysed from lifetime perspective. Screening is important; risk factors should be studied longitudinally.

Expert

Meeting

GenderBasic.

Promoting

integration of

sex and gender

in biomedical

and health

related research

What are sex and gender differences within metabolic syndrome and what are the consequences for diagnostic, preventive and therapeutic interventions?

The prevalence of MetS in women is rising in the US, but the rise is particularly high in women 20-39 years of age.

Some of the epidemiological differences between women and men are due to diagnostic differences between men and women.

Men are under-diagnosed, despite the same symptoms. "Candidacy is the biggest problem"; many people "believe the symptoms of a woman". "On the long run men have worse prognosis. So we need to look at both sexes". Women check their weight regularly, men don't, their overweight is not picked up. "Women have their weight checked in screening. Men leave their physicians with undiagnosed problems".

Examples of sex-related differences, concerning MetS are:

- Fasting glucose levels are different between men and women, leading to the inclusion of less women in prevention and treatment.
- Diabetes and pre-diabetes more prominent among women (6-fold) than in men (4-fold).
- Sex-related differences in glucose metabolism: women have higher glucose for each fasting glucose level.
- Interaction of hyperglycaemia and diabetes with CAD is sex dependent.
- Diabetes has a higher incidence in women, is associated with hormonal disturbances, and is a higher risk factor in women.
- Female myocardium is more sensitive to the consequences of diabetes than male myocardium.
- Sex hormones influence lipid metabolism: Oestrogen maintains a protective HDL cholesterol level in women.
- Visceral "male" fat seems to be a source of inflammatory mediators.
- Subcutaneous "female" fat seems to be protective. However after menopause women's fat distribution changes to a more visceral fat.
- Obesity and lipids related to estrogens: good fat (estrogens are protective) and bad fat: males have visceral fat, bad hormones while females have more: subcutaneous fat not so bad hormones. Abdominal obesity is typically male; more and more men are overweight. However postmenopausal women have adiposities similar to men. They lose the protective oestrogen.
- Obesity causes hypertension by gender specific mediators.
- "The shift from glucose to fatty acid metabolism is different in the females".
- In men diabetes and cardiac infarction seem to decrease.
- In this case there is no female protective system, diabetes is the killer, and smoking worsens chances in women.

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Clear shifting demographics and behavioural aspects (e.g. smoking is increasing among women) are changing the incidence and prevalence of MetS and CAD among the sexes

Mortality has decreased, more among men than women, but the incidence hasn't, which depends on treatment rates versus incidence. Treatment prevents infarctions because of by-pass operations. Cardiac infarction is an imparted revival, however women seem to survive.

"Diabetes and smoking are risk factors more prevalent with women". Studies show smoking went down together with myocardial infarcts, at least in women. There is an increase in type II diabetes, according to new studies. Oestrogen seems to be a protective factor.

In preventing MetS it seems that life style changes are important in women. Exercise is beneficial for women, but not so much for men.

What are the conceptual and theoretical challenges?

Many of the differences between men and women are sex-related. The underlying mechanisms are difficult to unravel. It will probably be even more complicated to address gender issues.

There are more similarities between men and women than there are differences.

"When discussing obesity from a gender perspective, we need to take country differences into account".

Several interesting aspects should receive more attention, because the number of people with MetS worldwide is enormous:

- Diet is of influence: we should eat more Mediterranean foods.
- Definition of the syndrome is important, but also of the symptoms.
- MetS has increased, however death by CVD has not increased, probably because of the preventive bypass operations.

It was pointed out that hormonal modification, by taking contraceptives or otherwise influences the symptoms and risk factors. It seems that developing pregnancy diabetes is a higher risk factor for developing diabetes type II.

“Candicacy seems to be a problem again” in diagnosis and treatment. CVD’s go largely unnoticed in women, because CVD is not prominent among women, therefore the symptoms are not recognized in time. However, MetS is stronger risk factor for CVD for women.

Metabolic syndrome is an exemplary life-style syndrome. Though the syndrome is multifaceted and intricate, trying to link all different aspects together makes it too complex to understand. Suggestion is to dismantle the metabolic syndrome into its smaller units and study those. Perhaps we should focus on the risk factors individually and not fight about the definition.

What are the ethical and financial difficulties concerning integration of sex and gender in biomedical and health related research?

“I was impressed about how much we know”, we should use this in treatment and prevention. Behaviour patterns are going to change in Europe. We need to look at lifespan, at different ages, and lifestyle, which is related to gender differences. We haven’t seen the consequences of these life style changes yet, but they are coming. Extreme scenarios are pressed by researchers and pharmaceutical industry.

Again researchers struggle with the reluctance of the pharmaceutical industry to finance sex-difference studies. For example “firm X” turned down all data directed at sex differences for their MetS drugs. There is a vast difference in the research, evidence, detection of CVD in women and men. We should aim at equal access to treatment for CVA.

“Rimonabant research was a scandal!”

What are the implications for research and policy recommendations?

We do not need more research. “We know so much, but do so little”. Let’s re-analyse the data.

Summary of main discussion points

- “We know so much, but do so little”.
- Metabolic syndrome is exemplary for life-style; though the syndrome is multifaceted and intricate, trying to link all different aspects together, makes it too complex to understand. Suggestion is to dismantle the metabolic syndrome into its smaller units and study those.
- Incidence of death by CVD does not necessarily have to do with the decrease in metabolic syndrome, but with the preventive treatment of bypass operations.

Paper 7

Methodological and ethical ramifications of paying attention to sex and gender differences in public health research. Prevention, health care delivery; focus on health inequalities with particular examples from Austria.

Abstract

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Much progress has been made in recent years towards achieving a more “gender conscious” approach to research and health promotional and preventive intervention. The profile of gender specific medicine has been further heightened by initiatives, statements and guidelines from, for example, the WHO, the Beijing platform for action and gender mainstreaming “Gender Good Practices” and the EU framework programme. Increasingly countries are paying more attention to gender issues, developing strategies and setting up projects to incorporate gender mainstreaming and gender equity, not only in medicine, but also in all walks of life. However, no country has yet managed to completely eliminate the gender gap. There is much work still to be done and much to be considered in terms of the ethical and methodological implications of gender orientated public health research and practical application. The question *Does sex matter?* has long since been answered with yes. It is time now to examine what we know and how we can best utilise and implement this knowledge in effective public health research and strategy.

As a multifaceted determinant of health, gender is inextricably linked with public health which assumes illnesses and health problems are influenced by physical factors, the social/cultural and health political environment. Inequities between men and women in terms of health, access to public health programmes and medical treatments have in part stemmed from the past lack of gender-differentiated research. This paper looks at the implications that incorporation of gender in public health research has for methodology and public health ethics. It aims to identify where potential disparities lie starting with education at medical school through to inequalities in access to health care and health care delivery and further discusses implications for policy. Finally some practical examples have been cited from Austria such as the compilation and use of gender specific health reports, which have proved an invaluable tool in the development of public health policy.

Only through gender-based research and public health planning and intervention can we achieve health promotion and prevention tailored to the specific needs of men and women in the 21st century.

Gender *Specific* public health strategies have a major responsibility to meet the societal needs and to contribute to the societal value of health research.

Comments

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Introduction to comments

There is increasing evidence from all field of health research, meaning both the biomedical and social side, that risk factors, biological mechanisms, clinical manifestation, causes, consequences and management of disease may differ between men and women. In such cases, health promotion, disease prevention, treatment, rehabilitation and care-delivery need to be adopted according to women's and men's differential health needs. Not doing so may have negative impact on the health of both women and men and gender-based inequities in health might even increase.

There is also a consensus among health researchers, that physiological differences between men and women are not confined to the reproductive system and the possibility of gender differences must be considered in all areas of health research. In addition to physiological differences that may or may not be linked to the reproductive system, research must also investigate the different experiences of women and men that underpin health-seeking behaviour, health status and access to both material and non-material resources.

Although it is well acknowledged today, that good public health research that seeks to understand the origins of disparities in health between women and men needs to analyse the complex ways in which biological and social determinants interact, gender biases and gender imbalances in health research continue to create a vicious circle that downgrades and neglects gender perspectives in health. The key issues that need to be discussed are 1) what are the most common gender biases and imbalances in health research, 2) what are the root causes of these biases, and 3) how can we address these.

What is the objective of the review paper?

The title of the paper suggests, however, that the review would focus on "methodological and ethical ramifications of paying attention to sex and gender differences in *public health research*". My interpretation of the second part of the title was that the issues listed there would also be reviewed from a *public health research* perspective. Thus, I expected to see a review of, for example, how sex and gender differences are taken into account in *research* on health care delivery, rather than a review of actual differences in health care delivery between men and women. When reading the paper, it became obvious that the review is not only focussing on public health research issues, but also undertaking a review of concrete public health policies and programmes from a gender perspective.

Need for conceptual clarity

Sex or/and gender differences in health

Although, in the title "sex and gender differences" are mentioned, there is no explanation in the text of the fundamentally different meanings of these terms and it is not clear what implication these terms have for public health research and for public health policy. The authors use the term "gender differences" when they probably mean "sex differences".

The term "*gender*" means the socially constructed distinctions between women and men in access to and control over resources and knowledge, their decision-making power in the family and community, divisions of labour and occupational segregation as well as the roles and responsibilities that society assigns to them. The concept of gender allows us to distinguish and comprehend the deep, but modifiable, social basis of differences between women and men apart from the seemingly obvious biological or sex differences (i.e. differences due to e.g. chromosomes, internal and external sex organs and hormonal make up).

Sex differences in health are best understood through health research *downstream* into the mechanisms of human biology and the clinical issues of how men and women cope with disease and disabilities. Such research traces the psychological mechanisms by which specific risk factors or risk conditions generate/cause different diseases in men and women.

Gender and health is best understood by health research *upstream* into the mechanisms of society. Such research generates knowledge about the social context and social position and their relationships to health, so that it becomes possible to consider the impact of macroeconomic and social policies on life chances and ultimately on health status for men and women.

While the individually oriented biomedical research produces knowledge that is predominantly needed by the health care sector for curative treatments or individual health advice, research concerning health differences between men and women or subgroups of men and women on the population level allows us to study determinants that are very often outside the direct control or influence of the individual.

Research “upstream” provides evidence on the social origins of gender inequities in health and highlights the need to tackle the root causes of poor health, not just the symptoms. These social causes or determinants often need to be tackled on the societal level, requiring actions from a broad range of sectors, not just from the health care sector.

The distinction between the concepts “sex differences in health ” and “gender differences in health” is important because it can guide measurement and hence accountability for the effects of different policies and actions, furthermore a clear definition opens up for alternative perspectives and solutions to health research and policy. Since gender and gender inequities are the outcomes of social processes, they can be challenged and changed.

At the same time it is important to remember that sex and gender often operate together. Differently from other social determinants (e.g. class, race and ethnicity), it is impossible to ignore biology when considering why health outcomes for women and men may be different. For example, how much of women’s vulnerability to HIV infection is due to female biology and how much can be attributed to girls’ and women’s lack of power in sexual relationships? Investigating the complex ways in which biological and social factors interact to impact the health of women and men should be a basic element of all health research.

Lack of attention to the intersections between gender and other social determinants of health

There is insufficient attention in the paper to the interplay between sex, gender and other social factors (e.g. socioeconomic group, race and ethnicity) in the social patterning of health. Neither men nor women are homogenous categories. This recognition is crucial for health research and policy since addressing intersecting stratification processes would considerably improve our ability to understand and act upon the mechanisms that produce and maintain gender inequities in health. It is well known for instance that health outcomes for poor men differ from those for poor women, and furthermore, from those for poor black women. Moreover, evidence suggest, that women’s lower social autonomy and structural disadvantage exacerbate their susceptibility to HIV and other diseases. This issue would be very relevant for a discussion related to the methodological and ethical ramifications of gender inequities in public health research and it would be valuable if one of the recommendations in the paper would promote a more systematic examination of the interaction between gender and other social factors.

“Gender specific medicine” and “gender oriented public health”

The paper uses “gender specific medicine” and “gender oriented public health” interchangeably, without providing a clear definition of what these mean or embrace. Is the focus in the former on individuals and in the latter on populations? A clear explanation is needed, moreover what implications they have for research and policy. I am not familiar with the term “gender specific medicine”.

Gender, Public Health & Ethics. Ethical and methodological considerations in Public Health research.

The two considerations, the ethical and the methodological, are not separated well. For example, a review of methodological considerations in gender and health research should definitely cover and highlight issues such as: 1) sex-disaggregated data that also include indicators of socioeconomic position and other social determinants are not always collected by individual research projects and/or larger data systems, 2) some current methodologies inadequately capture women’s and men’s realities, 3) some current methodologies systematically underestimate women’s burden of disease, 4) women are not adequately represented in medical research and clinical trials for new drugs, just to mention a few methodological issues.

Where do disparities start? Medical school?

However, reading the section it becomes obvious that it is about the imbalance in career opportunities for men and women in the medical profession, but it is also about engendering medical teaching

Health care delivery & health inequalities

Explanation is needed why “health care delivery” is discussed in the paper, right after discussion of gender balance in the medical profession and medical curricula. Do the authors try to give an illustrative example of ethical and methodological considerations in public health research in relation to health care delivery? It seems not to be the case. Moreover, the section is dealing with other issues as well, not just health care delivery. It deals also with health seeking behaviour and attitudes to health, occupational health in general (rather than provision of occupational health services). Thus, the title does not reflect the content.

Policy and gender

It would be useful if the authors in this section could list or give examples of policies and measures aiming at engendering health research. Currently, the emphasis is on policies to engender health programmes.

For example, the Swedish Medical Research Council has announced in 1998 that gender should be taken into account in the process of doing medical research. A policy document, issued at the same time (in 1998), authorized research ethics committees to require additional information concerning choice of study population. The Council adopted a policy in 1999 that one-sex-only research designs in principle would not be funded. This policy was introduced to counteract a common practice that excluded female subjects from study populations.

Moreover, The Swedish Research Council has a committee for gender research, whose task is to coordinate efforts of the research councils with regard to equality, gender research and interdisciplinary approaches. Thus, the committee is promoting gender research on its own right, which means that efforts are made to continue to develop its own theoretical and knowledge base. At the same time, the committee strives for that gender aspects be mainstreamed in different academic areas and for making gender visible in different research areas. In the Government Bill (2004/05:80) "Research for a Better Life" an increase in resources for gender research at the Swedish Research Council by 12 million over the period 2005-2008 was proposed.

Recommendations

If the paper is to focus on gender and public health research and research policy I could think of several recommendations, such as:

1. collection of data disaggregated by sex, socio-economic status, and other social stratifiers in both individual research projects and in routine data collection systems at regional and national levels,
2. sensitising data managers and systems to the need for basic disaggregation of data by sex and presentation of data that allow analysis of the intersections between gender and other social determinants of health,
3. mapping and analysing the disease burden - incidence and prevalence of different health problems - among women and men and among girls and boys (epidemiological surveillance),
4. stimulating and promoting gender sensitive health research,
5. addressing gender imbalances in both the content and processes of health research as well as within the research community by e.g. building capacity of researchers for gender-sensitive research analysis; requesting papers to present data disaggregated by sex and to explain observed differences adequately; promoting operations research to translate broad knowledge about gender and health into practical guidelines and to evaluate interventions from a gender perspective; including women in clinical trials and other health studies in appropriate numbers; including gender experts in ethical and other review boards and editorial boards to ensure that gender dimensions of research projects are not missed out; requesting papers to present data disaggregated by sex and to explain observed differences adequately,
6. promote multi-disciplinary research agenda on the linkages between gender issues and health, and
7. strengthening the role of women in research.

"Gender medicine and public health must fulfil some of the same criteria as in clinical medicine". I strongly disagree with this statement. The authors have emphasized correctly in several places how important it is to work inter-disciplinary in public health. This entails that we need to use a variety of different methodological approaches and will work in a variety of epistemological traditions. These disciplines work upon a highly pluralistic evidence base. In the context of public health research with a gender perspective methods include, but are not limited to, case studies, large scale data sets, historical reports, qualitative data drawn from interviews, focus groups, or observation, social surveys, economic and econometric reports, epidemiological data, evidence synthesis, systematic reviews, other forms of literature reviews, meta analysis, and accounts of lay or tacit knowledge. An evidence based approach in this context does not mean that we should privilege a reductionist biological epistemology of evidence drawn from randomized controlled trials, as suggested in the paper.

Discussion

What is the state of the art as regards integration of attention to sex and gender issues in the methodologies of public health research?

We should question the biomedical paradigm in Public Health that the authors use (i.e. proposition of using RCT in Public Health research). There is a need for reflecting on process instead of outcome of interventions. The authors propose "Gender specific health", but what does specific mean?", and are we not drifting away from population based interventions. Perhaps the focus of gender in public health should be on structures in society.

What are sex and gender differences within public health and the consequences for preventive interventions?

In public health the focus is largely on lifestyle factors, which differ between men and women. “Better income improves health for men but not for women”. Women have more control in the homes, men outside the homes. “We may speak of an epidemic of risky behaviour in men”; risk-taking behaviour among men is much higher compared to women.

What are the conceptual and theoretical challenges?

Public Health is population based instead of individual based, so the authors claim. “Being a man or a woman (sex) is a health determinant”. Gender has a wide range of aspects and so does public health.

The reviewer of the paper had a very different view:

Public health has its origins in biomedical view. The biomedical model is a justification of inequity. Gender biases and imbalances downgrade importance of gender perspective. What are the most important biases and sources? The biomedical model (in operation for over 100 years) focuses on the biological differences between the sexes. Females are reduced to their reproductive functioning: i.e. women have been perceived as biological fragile, excluded from social life, diseased. Biological differences between women and men have been justified, but social differences should get more attention.

Gender bias in research process is rooted deeply in our culture: we need to question “what are the root causes? How do we address them?”

There is conceptual ambiguity: are we speaking of sex or gender differences? Gender differences are intertwined in societal processes/forces. Biological differences are stable, while gender differences are dynamic. We need to piece out the differences. Women are very different from one another: income/class etc. There are many social determinants for ill health, e.g. secure democracy, childhood, economic situation, work environment. These can be studied using a gender perspective. An intersectionalist approach is perhaps a better angle; women are heterogeneous, though structural disadvantaged. “A larger change may be invoked by addressing roles than biology”.

Why focus on differences? Gender based violence (with men as victims) will never be brought to light if we focus on women as the victims. Why not focus on gender structures?

Another issue to be discussed was whether Public Health can be seen as population-based or individual-based? Public health is population based, however target groups are identified, at-risk populations, to develop the most appropriate intervention.

Which practical tools do researchers need to ensure a better integration of sex and gender aspects in public health research?

Suggested by the authors is to use (Austrian) Women and Men Health Reports as tools to be translated into practice into sex-specific interventions. These reports and interventions are also linked with industry, politics and policies. Also they propose a creation of gender specific medicine: separate medicine practice for men and women.

What are the ethical and financial difficulties concerning integration of sex and gender in public health?

Ethical issues regarding public health are about the notions of autonomy and self-determination. Accountability and victim blaming should be addressed. “Incidence does not make decisions, people do”. By creating specific target group interventions, we need to question who is held responsible for their health problems. Are we blaming the at-risk people who might have risky behaviour? Or are we addressing larger social inequalities?

“It’s a public responsibility to battle social inequalities”. Policy needs to tackle structural determinants of health. One of the aims of public health is the creation of good and secure work environment.

What are the implications for research and policy recommendations?

One of the concluding remarks in the discussion was:

Public health should be approached multidisciplinary internationally and nationally, which means multiple epistemological methodological criteria: different ways of getting the truth, public health epidemiology is only one of them. A non-result is just as important as identifying a difference. Public health should provide criteria for clinical research. There is a variety of approaches to study effectiveness, evidence based approaches, they don't need to be RCT's.

Not only should the medical field be schooled in gender sensitisation, other professions need such schooling as well.

Summary of main discussion points

- Health reports as tools?
- Public Health population-based or individual-based?
- Question the biomedical paradigm in Public Health which the authors use (i.e. proposition of using RCT in Public Health research).
- Need for conceptual clarity.

Paper 8

Anxiety disorders: a gender test case within mental health (care) research.

Abstract

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Anxiety disorders are more prevalent among women than among men. The present paper is aimed at investigating to what degree current theories and treatment of anxiety disorders pay attention to gender. To that end, we systematically scrutinized the literature, mainly the Psycinfo and Pubmed databases, but also performed several additional searches. The main themes in our searches were current prevalence figures of the several types of anxiety disorders, and co-morbidity; theories explaining anxiety disorders; and studies on treatment effects.

Our main conclusion is, first, that more attention should be given to gender-relevant individual differences leading to anxiety disorders via learning processes. Attachment experiences and resulting affective-cognitive conditions in terms of attachment styles and autonomy-connectedness seem promising but firmer empirical evidence has to be established, also concerning possible processes between these conditions and phobic fears and avoidance. Secondly, large discrepancies are observed between the attention paid to the sex differences in prevalence of anxiety disorders and their possible background on the one hand, and the scarce attention given to these differences when it comes to treatment, at the other hand. Prevention and treatment might gain efficiency if the available knowledge on sex- and gender specificity of aspects of anxiety disorders would be implemented into practice. Simultaneously, treatment effect studies should be improved by paying more attention to sex and gender throughout the research process.

Comments

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1. The review

The review focuses on anxiety disorders and its subtypes, addressing the question to what degree current theories and treatment studies pay attention to gender.

It provides prevalence figures of various anxiety disorders, reviews potential sources of gender biases, co-morbidity, three theories to explain differences in the prevalence of anxiety disorders, summarising the respective findings in the Multi-Facet Gender and Anxiety Disorders Model developed by Bekker herself. Finally, sex differences in treatment effects are reviewed.

The review relies on a systematic literature research, using the databases Psycinfo and PubMed, the reference list of included articles and on some further detailed searches on particular aspects.

Gender is defined as “the socio-cultural ascriptions defining people’s identity in relation to sex”. *Sex* is defined as “the biological features distinguishing male and female animals and human beings”, and is used as a difference category denoting women and men.

Main results:

- Consistently, higher prevalence rates are observed in women, overall and for subtypes, across lifetime, across various countries, and independently of the specific health care settings where the figures were obtained.
- Potential sources of gender biases by measurement / instruments are relevant, especially reporting bias.
- Co-morbidity is described among subtypes of anxiety disorder, with major depression, personality disorders, and substance abuse. There seems to be a closer link for women than for men, and there is some evidence that anxiety disorders are preceding major depression.
- Evidence for the contribution of three theories to explain gender differences remains rather limited, most of it stems from the *gender role/socio-economic gender role perspective*: there is evidence from ecological and cross-sectional studies, that in Western societies, increasing employment demands are associated with a decrease in phobia, that being unemployed as well as not being married is associated with higher rates of anxiety disorders (stronger in men than in women), and that in countries with clearly distinct social gender roles, a high degree of Masculinity-Femininity predicts higher national levels of agoraphobic fears. However, no evidence was found on an individual level. As to the *learning perspective*, exposure to childhood violence is strongly associated with the prevalence of anxiety disorders but explains little of the overall gender difference in prevalence. As to the *theory of attachment and schema*, earlier studies looking at maladaptive schemas failed to report or explain sex differences, while preliminary findings of more recent conceptualisations such as low autonomy –connectedness show associations with anxiety.
- Empirical research on the influence of sex/gender on treatment appears to be rare. Pharmacotherapy and cognitive behavioural therapies contribute to the improvement of anxiety disorders in women as well as in men. Studies on psychosocial treatment are of lacking quality. Most meta-analyses don't address sex distribution in the studies.

The review concludes that more attention should be given to individual differences leading to anxiety disorders via learning processes and recommends focusing on attachment experiences and styles, and on autonomy-connectedness. It furthermore emphasises the lack of attention given to sex differences in prevalence of anxiety disorders when it comes to treatment.

2. Strengths, Key points, Critiques, Suggestions

The review, restricting to a particular mental health disorder and to a specific question, namely, to what degree can current theories explain sex differences in the prevalence of anxiety disorders, is adopting a very systematic procedure to review existing research on the question raised. It includes an excellent section on measurement biases. It is mentioning not only differences but also pointing to similarities between the sexes. It denotes several interesting aspects where culturally embedded phenomena and gendered notions may underlie the conception of a person as well as of anxiety

From prevalence to determinants:

A strength of the review is to go steps backward in the etiologic chain, exploring the differential contribution of determinants on the prevalence of anxiety disorders. Thereby the review is focusing on processes of disease causation that are themselves linked to gender and might explain differences in the prevalence figure of anxiety disorders. A synoptic model conceptualises the reviewed determinants in 5 groups (body; differential diagnostics, statistics, treatment; sex differences in exposures; person-related vulnerability factors).

Potential sources of gender biases by measurement or assessment:

Expert

In an excellent section, the evidence for a number of potential sources of gender biases is reviewed, such as for

Meeting

- Self-reporting and lower willingness to report symptoms of anxiety in men (evidence given).
- Men's generally higher level of alcohol misuse versus women's higher use of anxiety-reducing drugs or behaviours (relevant for agoraphobia).
- Sex-specific division of socio-economic roles that might hamper avoidance tendencies in men (relevant for agoraphobia).
- Employment status and overrepresentation of specific demographic groups (such as those not being in the labour market, fulltime parents) (relevant for social phobia).
- Diagnostic systems differ with regard to gender differences of PTSD (DSM-IV showing no gender differences while according to ICD-10DCR, women are twice as likely have PTSD).

GenderBasic.

Promoting

integration of

sex and gender

in biomedical

and health

related research

These measurement biases relate to very different phenomena. Some are due to measurement problems of instruments (such as DSM-IV versus ICD10). Others arise from differential reporting behaviour that is itself embedded in a cultural context of gendered notions and gendered “mandates” for women and men in a society. Therefore, the latter may actually be informative for how gender differences arise and also for the gendered nature of the disease itself. Therefore, reporting biases might be treated as an issue separate from instrument/diagnostic biases. In the synoptic model given by Bekker and van Mens-Verhulst, “willingness to report anxiety” might therefore as well be shifted from “Differential diagnostic/statistic/treatment” to “Gender”.

Reviewing gender theories:

The extensive review of the explanatory impact of theories for gender differences in the prevalence of anxiety disorders is innovative. Strikingly, the resulting evidence is not overwhelming. While this may not surprise so much, when the original theory is gender neutral, as for earlier attachment theories, it is more disturbing for theories that explicitly aim to address the role of gender. The review relies primarily on three theories. It does not include theories focusing on masculinity and on gender relations, which might enrich the insights from chosen theories. The same holds for aspects of power and hierarchy. Clearly, for the understanding of complex causation paths, there seems still a long way to go.

Some questions in this regard:

- Is there a particular problem when theories are “tackling too big” (when they address multilevel phenomena)?
- Do we necessarily fail, when the conception of a disease is gendered (which may be the case for anxiety disorders)? Or, when the underlying conception of a person and of subjectivity (as detached, autonomous, separate) is gendered? Or, if we are confronted with gendered meanings of situations?
- Are our ways of analysing not adequate?
- Is there something important that was not considered?

Explanatory model – Gender Analysis:

The main focus of the review is a gender difference grid, addressing the question, to what degree current theories and treatment of anxiety disorders pay attention to the unequal proportions of anxiety disorders in both sexes and explain them. Nevertheless, there were numerous times, when this grid was complemented by discussing not primarily differences but gendered notions or gendered meaning of behaviours (see e.g. with regard to gendered nature of autonomy and connectedness), thus going beyond a gender difference approach.

The explanatory model includes socio-cultural and socio-structural factors (such as gendered meanings of feared situations; unemployment), as well as individual determinants. There may be diverging views on where to situate certain determinants within the five groups of determinants (e.g. shifting “Gendered meanings of the situations that are feared and avoided” to “Gender”, see also above). Furthermore, the arrows between “Body” and “Gender” need to be reciprocal.

In this conception of the model, it is also not clear, how different levels (micro-, meso-, macro-levels) may interact.

It might be worthwhile to organise a workshop particularly focusing on conceptualisations of explanatory models, including also the work of Nancy Krieger who has worked on embodiment as a multilevel phenomenon and on connections of gender, sexes and health. Or including Sara Arber who is addressing that gender necessarily operates in interaction with other variables and who provides new ways of dealing with confounders. We might also learn from the ongoing developments in Eastern Europe (see Kawachi, Kopp et al). The integration, however, of sex/gender theories and medical conceptions of health and disease remains a challenge (see also Kuhlmann and Babitsch).

Comments

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(These comments were not discussed in the meeting)

At a general level, the review has located a very substantial part of the literature relating to sex differences in anxiety disorders, and has discussed most of the hypotheses underlying these observed differences in a very clear and readable way, although focusing principally on learning theory models.

The interaction of bio-environmental factors produces sex-specific reactions to external stimuli, much of which may be reversed by cognitive and behavioural therapies. This logical sequence may have been easier to follow if the discussion had been organized in two parts (empirical observations and aetiological models with sub-sections) for example as follows

- A. Empirical observations of sex differences
 - i) epidemiological evidence from population studies
 - ii) evidence of sexual differences from clinical and cohort studies
- B. Aetiological models of anxiety disorder which underlie sex differences
 - i) genetic differences e.g. sex differences in the prevalence of alleles linked to neurotransmitter and HPA axis functioning
 - ii) biological differences related for example to hormones and cortisol secretion
 - iii) classical and operant conditioning paradigms
 - iv) social role expectations
 - v) sex differences in environmental exposures to adverse stimuli
- C. Current conceptualisations – on the basis of present knowledge what is the most likely chain of events

With regard to empirical observations, the review has covered the major prevalence studies and put these together in clear tables, but does not touch on incidence rates. Incidence refers to the number of new cases appearing in the population within a given period (usually presented as number of new cases per thousand over a one-year period) as opposed to prevalence, which is incidence X disease duration i.e. the number of cases that exist in the population at one point in time. If we only have prevalence data we do not know whether there are more cases of anxiety in women in the population because the disease occurs more frequently in women, or whether in fact the rates for men and women are the same but in women the disorder persists for a longer period of time (which is what some of the literature cited further on in the paper suggests e.g. Yonkers et al. 2003). This is clearly an important issue in the present context. Also with regard to population studies, their short-comings are not sufficiently noted in this review – in particular the low acceptance rates – epidemiological studies often have response rates as low as 30%, and persons with common psychiatric disorders are more likely to refuse to participate, which may lead to biases in prevalence calculations, especially if men with anxiety disorders are least likely to be included. Is there any evidence for this?

Concerning the aetiological hypotheses proposed, the genetic and biological literature is not really adequately covered – I think the authors probably needed a bit of a hand here from a neurobiologist as it is rather a specialized field and not easy to decipher as an outsider. A better understanding of underlying biological/physiological differences (genetics, hormones, imaging studies of problem solving and heightened sensitivity to emotional clues in women etc) is important for interpreting more complex social behaviours. Incidentally the authors state that there is no work in human studies on serotonin gene mediation of environmental stressors – in fact this area has been well developed in recent years following the original study of Caspi published in Science 2003 that 5HTT alleles determine whether or not a stressful environmental event will lead to depressive symptoms. Do women have higher frequency of vulnerability alleles or do the same alleles function differently in women? I realize these considerations make for very complex models but there is a real danger in this field of oversimplifying the causes of sex differences e.g. concluding that anxiety is simply learnt and can thus be unlearned – too many questions are presently unanswered by learning theory alone e.g. why don't all women exposed to adversity develop anxiety disorders and why do behavioural therapies have differential success in women?

With regard to causes, the review has very much focused on the classical conditioning model, which is of course important, but not sufficient. Operant factors are also clearly important; women are encouraged to be fearful (look under the literature concerning learned helplessness and sickness behaviours). The work of Gavin Andrews in Australia in this area is worth citing as they have also put into place desensitisation programmes for anxiety reactions as part of the school curriculum which focuses particularly on redressing this type of learnt behaviour. See www.climateschools.tv .

The authors need to exercise a little more caution in their concluding statements – for example they note that socio-economic status, being alone, unemployment etc. are risk factors for anxiety disorder, however as many cases have their onset in late childhood and adolescence it is probably more likely that the contrary is true i.e. that anxiety disorders lead to poor social status etc. Interventions based on cognitive and behavioural interventions should of course be encouraged, but these may be more intelligently applied if there is further understanding of underlying biological mechanisms e.g. are there genetic sub-types of women who may better benefit from a given type of therapy, is genetic screening likely to be useful for implementing preventive strategies before symptoms occur as in the Australian programme, are hormonal factors involved and can HRT help etc. A final point which has not been raised is whether high anxiety levels might not have a positive role in women, for example does heightened reactivity to the environment enhance fright/flight

mechanisms which may once have been protective for mother and child? Before removing certain behaviours from the human repertoire we might consider if in some instances they are adaptive, at what threshold level they are pathological and whether this threshold should be different for men and women. This could in part be determined by reference to associated disability rates.

Discussion

What is the state of the art as regards integration of attention to sex and gender issues in the methodologies of clinical research?

Mental health research is conducted using self-report questionnaires and surveys. We should keep in mind the bias of using these instruments. Bias is induced by self-report questionnaires, low willingness to participate, masculinity (men generally won't admit to having psychological problems).

Change models that are used lack empirical evidence, "there is not much constructivist evidence". We need more empirical evidence.

What are sex and gender differences within anxiety disorders and what are the consequences for diagnostic, preventive and therapeutic interventions?

The outcome variables in the model are sex differences in prevalence of anxiety disorders. Symptoms of anxiety are more severe in women. But there exists general underreporting in men. Gender role socialization induces these differences in seeking help.

Women are "allowed" by society to show fear and anxiety. That could explain the higher prevalence of anxiety syndrome among women. Men on the other hand are not allowed to show fear and anxiety; therefore they internalise fear, which may then erupt in (domestic) violence and higher incidences of male suicide. Masculinity is not compatible with showing emotions. Men tend to cope with alcohol abuse. Co-morbidity is different for women and men.

Differences in access to treatment for men and women are widespread. More women receive treatment. Boys and teenagers socialization produces inability to articulate feelings, which could lead to domestic violence and male suicide. Historical research shows that men are usually not included in the diagnosis. Acting out anxiety is different because of this gender socialization; women tend to harm themselves as a plea for help. More men commit suicide.

Remaining questions: Could anxiety also be a protective mechanism for women

What are the conceptual and theoretical challenges?

Up to now there are no gender sensitive interventions for anxiety disorders and scarce attention has been paid to differences. Gender interacts with many variables.

In psychiatry there is an overrepresentation of specific groups, a bias.

The authors present a multifaceted Gender and Anxiety Disorder Model, which is based on 3 theories:

1. Learning theory
2. Sex role theory
3. Attachment and schemata theory: also similarities between the sexes and focus on gender issues, sex specific issues

The model contains "body: male/female", "gender: masculinity/femininity", differential diagnostics", "sex differences in exposure", "person-related vulnerability factors" which all influence "sex-differences in prevalence of anxiety disorders".

"This model was an attempt to develop gender sensitive measures", using gender-neutral theories explicitly addressing gender. However only femininity or masculinity are named in the gender circle, why not the actual gender issues.

In this model autonomy has been relabelled to the continuous concept "autonomy/connectivity", taken from attachment theories. Autonomy is a gendered concept. "The agoraphobic woman is the ultimate dependent woman". Phobic women score high on dependency scores.

Can we address gendered issues, if 'anxiety' is a gendered meaning?

"Gendered" what is the exact meaning? The evidence of gender-related factors in anxiety is not overwhelming.

This model could be seen as an explanatory model to explain gender difference.
Gender role perspective in the model: Focus selectively on the stressful aspects of gender roles. People are different and suffer different from different aspects of their gender role. So “all the stereotypes are still there”

“Are there any protective measures against developing such a disorder? Social support, social networks?”
Social support or social networks have consequences for the development of disorders. “Only when you regard a disease as a category, one can wonder why not gender roles result in more disorders”

The feasibility of the model is questioned. Theories are multilevel and multifaceted.
Not only is the model very complex there is conceptual complexity: gendered notions, gendered meaning, and gendered differences. Focus is only on the socio-psychological level. Whereas other papers lack a more socio-psychological point of view, this paper lacks biological evidence. Variables are multilevel. The biological perspective is missing from the model. There is biological evidence to suggest sex differences due to regulation of serotonin, sex-steroid levels, especially during puberty.
Research of depression shows that there is a biological contribution, albeit small. “Gender effects in depression cannot be explained by biological factors”

Socio- cultural, structural and individual factors are all in the model. All disorders/diseases are gendered and mechanisms are complex. “Many disorders are gendered in complicated ways.” “Interactions between several sets of variables exist. These connections exist on multi-levels”. Sex-gender interaction is not unidirectional. How do micro and macro levels interact? “Macro level is important, but also at the micro level do we find the most interesting things”. At the microlevel, or individual variables, there is intensification of the disorder. There is a connection between anxiety and allergy, and an interaction between immunology and psychological conditioned responses. “Allergies and panic attacks can be conditioned”.

Summary of main discussion points

- Focus is only on the socio-psychological level. Whereas other papers lack a more socio-psychological point of view, this paper lacks biological evidence. Variables are multilevel.
- Gender role, sex role theory, gender role socialization:
Women are “allowed” by society to show fear and anxiety that could explain the higher prevalence of anxiety syndrome among women. Men on the other hand are not allowed to show fear and anxiety, therefore they internalize fear, which may then erupt in (domestic) violence and higher incidences of male suicide.
- There is gender bias in self-report (questionnaires and surveys are the main instruments).
- Variable of “autonomy” is translated to “autonomy/connectedness”.
- Could anxiety also be a protective mechanism for women? Or a way to call on social support, which is also more available to women than men?

Paper 9

A tool for distinguishing gender research from gender difference research – examples from work-related health.

Abstract

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Background: The awareness of gender research is low in academic medicine and the concepts of ‘sex’ and ‘gender’ are often used synonymously. The number of medical articles with focus on gender and women is increasing, while the number of articles based on gender research is still quite small.

Aim: The aim of this paper is to identify possible problems and /or challenges with regard to the concepts of ‘sex’ and ‘gender’ in work-related research as well as to propose a tool to implement the theoretical insights. The tool will be used to distinguish gender research from gender or sex difference research in relation to the public health consequences of unemployment and labour market position.

Results: Gender research differs from sex/gender difference research in several important ways. While gender research questions the dominating epistemology of medicine, sex/gender difference research is performed within the dominating paradigm. While gender is an analytic category and structural analyses of gender relations are central in medical gender research, the level of analyses in sex/gender is often as a variable on the individual level in gender difference research. Masculinity research constitutes a dynamic part of gender research. However, in sex/gender difference research men, as well as women, are analysed as one of several variables. Through questioning the existing field of knowledge, gender research – with its base in power analyses and theoretical development – can lead to new knowledge about men and women. There is vigilance in gender research with regard to the risk of exaggerating differences between men and women; these differences are either biomedical or socio-cultural in nature. In gender difference research there is a risk for essentialism, i.e. the tendency to regard differences between men and women as constant, general and unimpressionable.

Conclusion: In this paper I have developed a model which may be used to distinguish gender research from gender difference research. The model may become a practical tool for making such comparisons. However, the questions in the tool need to be refined and further developed in an active dialogue with gender researchers.

Comments

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The article has two aims:

1. to identify possible problems and/or challenges with regard to the concepts of ‘sex’ and ‘gender’ in work-related research
2. to propose tools to implement the theoretical insights

Reading the introduction the background for the aim is not well structured; the reason to focus on work-related health is not clear. Political issues are mentioned in the introduction but my advice is to restrict it to scientific gaps. Describe more the need to conduct this study. For which audience the manuscript is directed? The relevance for the development of a tool is not clear; who will be the users for the tool and what are the implications for using it?

It is mentioned that 'the need to analyse the interplay between sex and gender is of special importance in medicine where biological factors obviously are of importance...'. In medicine, not only biological factors are central but more and more the biopsychosocial models are used and applied; so it is more than only biological at this moment.

The choice for unemployment as parameter for work-related health is disputable in the light of gender and gender difference research; why unemployment as dependent variable and not for instance work-related ill health?

The search strategy used (in the method) is not based on a specific research question; so, formulate, based on the aims one or two research questions.

What is the used method for the second aim?

It will be better to categorize the results conform the categorization mentioned in the method and the two aims.

Ill health is coming up as item and explanations for the findings are described.

What were the theoretical insights for the tool? For whom will be the tool useful or in other words what is the relevance of the tool?

Start the discussion with a short summary of the main findings based on the two aims. What are the importance of your findings and the interpretations of your results?

Describe also the restrictions of the tool (it is only based on work-related health literature).

Discussion

What is the state of the art as regards integration of attention to sex and gender issues in the methodologies of work related health research?

The author proposes a tool to distinguish gender research from gender or sex difference research. In gender research, gender is seen as an ongoing process, it is an analytic category and analysed on a structural level. In sex or gender-difference research gender is often equated with sex and is used as one of several variables. Gender is analysed as an individual characteristic. Gender difference research is about comparing subgroups (men and women). Studying gender as a variable provides great risk for exaggeration of differences between the sexes.

Both critique and praise was given at the meeting: The proposed methods are unclear and not transparent and lack relevance for work-related health. Unemployment is used as an outcome variable. Why not use a list of work-related problems, other than unemployment.

Many feel that sex difference research is still necessary, but it could and should be incorporated in a more extensive gendered research model.

The model was praised for being excellent and thought provoking. Gender research encompasses a new Epistemological model. It is another point of view. Gender is NOT a variable but an analytical category. It does not study gender inequality or sex differences. This new epistemological knowledge is not extra (different) knowledge; it is a new process of gathering information. The significance of gender roles is criticized in gender research. To study gender and all of its facets, the paradigm of sex-difference research needs to change. Gender research is challenging the existing paradigm. It could be a theoretical framework for the rest of the papers.

The model makes men visible in an important way. Previous research was either on men or taking men as reference points. The role of man and "Masculinity" as a construction is a social interpretation, and often related to health issues. Focus should be on the role of masculinity and femininity in risk behaviour and/or health seeking behaviour. "We need to look at the role of femininity/ masculinity in the area of care - risk taking, help seeking. We are leaving out large areas of health determination".

There is "a need to recognize what masculinity is". Still a hegemonic idea of a man/masculinity is in existence with attributes like self-reliance, control and strength: 'terrible attributes', which make men prone to suicide. Masculinity incorporates strength, violence, decision making, not seeking help, not sharing, no tools to manage problems resulting in drugs abuse, violence, and suicide. "Masculinity and nationalism came together after 9-11". Perhaps men take more risks now, because of the new honour codes. We need to translate that into medical research.

What are the conceptual and theoretical challenges?

“How can a medical faculty have a claim on knowledge while they don’t know anything about gender?”
“When gender research was developed, it was a political investment”. Gender has no definite boundaries: it is a gradient. In medicine the concepts sex and gender are mixed up.

In this paper the models for work-related health, distinguishing gender research from gender difference research, are described. The table is a start of the debate about assumptions of the influence of social context. It can be used as a tool to identify gender research.

Furthermore, the debate was on whether gender in occupational health consists of different issues than in biomedical research. In the areas of research, language problems persist: we need to find translation between gender studies and the medical field; we need to bridge gender to biomedical and health research.

Gender difference research, comparing subgroups of men and women, could be used as a starting point for gender research.

Occupational health data show sex differences are relevant in research. Certain jobs have specific work-related health problems, difference between women and men are scarcely studied. There is higher prevalence of disorders among specific occupations; therefore we need to look at the workplace, at the context. Adaptation of workplaces, an intervention for occupational health problem, is usually based on men (e.g. garbage collectors). Work-related health issues are missing in the review.

There was a debate on the possible normative dimension of the proposed model. Can ‘gender research’ be separated from sex difference research? It seems that a stronger statement of what we can use the model for is missing. “The model suggests gender research is better than sex difference research. The author claimed that the model distinguishes gender research from sex/gender difference research from a gender researcher’s perspective.

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Which practical tools do researchers need to ensure a better integration of sex and gender aspects in work related health research?

The author agrees that the model is a suggestion which needs to be discussed and developed. “More should be written about the context in which the model was developed”.

The proposed table of the difference between gender research and gender difference research is a tool to identify gender research. The model is a meta-analytic tool, how can it be implemented? Can it be helpful in changing the environment? “I doubt whether such a meta-tool can create awareness in medical research”. It can help us to discuss what the appropriate way of investigating a certain problem. Gender and sex difference research is distinguished which in itself is a productive investigation.

There is a need for implementation tools.

“I think the model you have presented is interesting. But it is in the language of gender studies. Not for life-sciences. We need a lot of translation”. Terms like masculinity and femininity are unclear for some researchers. The theoretical model should be translated to a tool to be used.

Summary of main discussion points

- The model was praised for being excellent and thought provoking as well as for visualising an important theoretical issue, as for the socio-cultural development of masculinity as has been done in the model.
- Constructivist evidence is needed: arguments for a pluralistic epistemology.
- Distinction between sex-difference research (men and women as subgroups, gender as a variable) and gender research.
- Normative dimension of the proposed model? Can gender research be separated from sex difference research?
- Translation of the theoretical model to a tool to be used.
- The review is not based and specific for work-related health.
- It is not clear why the practical tool should be relevant for the work-related context.

Paper 10

Gender, a major player in the crosstalk between genes, environment and health.

Abstract

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Men and women share most of the genetic information; however, they have dramatically different disease susceptibilities which go well beyond the expected gender-specific diseases (i.e., cervical or prostate cancer). Sex influences susceptibility to nearly all common diseases that affect both men and women, including atherosclerosis and diabetes and their preceding risk factors, such as hyperlipidemia, insulin resistance and obesity. These are all known to be highly complex and multifactorial in their origin, involving genetic factors but also a myriad of environmental and behavioural factors which interact with the genetic component, which, in itself, is highly polygenic. This complexity underlies the poor replication obtained for most candidate gene association studies examining common diseases and their predisposing risk factors. There is already evidence about the different pharmacogenetic response to lipid-lowering drugs in men and women. However, pharmacogenetic knowledge deals with the population that is already diseased or at high risk of developing disease. Parallel developments are taking place in the area of nutrigenomics aimed to the health of the entire population. In this regard, information exists regarding significant gene-gender interactions for risk of diet-related diseases (i.e., obesity) as well as more complex gene-gender-diet interactions (i.e., perilin). However, we are still lagging behind in terms of replication of preliminary interesting findings as well as on the definition of the functional basis for these gender-specific effects.

Comments

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Nutrigenomics is a relatively young research field with high expectations for application in disease prevention. The paper of Ordovas provides important examples of the interplay between genes, disease susceptibility and dietary habits and the relevance of studying sex differences. The extensive examples refer to cardiovascular disease, including obesity as a major risk factor.

The results of nutrigenomics research contribute to a better understanding of well-known sex differences in the mechanisms and epidemiology of cardiovascular diseases. For example, the effects of various genetic traits that regulate the cholesterol metabolism interact with dietary and behavioural factors, thereby clearly demonstrating the complexity of the biological system and its clinical manifestations. Since the epidemiology of cardiovascular diseases is also closely related to the levels of female sex hormones, we are dealing with dynamic relationships between genes, behaviour and clinical effects. The lifetime perspective adds complexity to these interacting factors.

Although the paper of Ordovas suggests relevant questions for further research taking into account sex and gender related issues, a more basic approach is also possible. From this perspective it is necessary to reflect on how sex and gender play a role in various phases of research, for example regarding the defining of research questions, the models used, and the context of application of data. In my comments, I would like to reflect on these issues.

Given the relevance of sex differences in nutritional metabolism as shown by Ordovas, I wondered how sex and gender play a role in nutrigenomics research. A PubMed search on the term nutrigenomics revealed no hits in combination with either sex or gender. Using a limitation of the term female revealed 5 hits. The papers involved nutrigenomics aiming at improved fertility in cattle, a paper on leptin in breast milk studying its effects on the body weight of developing infants, a study of nutrigenomics in specifically treated diabetic

mice, a paper on the relationships between butyrate on changes in expression of genes involved in human colon cancer and a study of conjugated linolenic acid supplements on insulin sensitivity in diabetes type 2. Interestingly, the abstracts of the latter three papers did not refer to any sex related aspects. Furthermore it is worth mentioning that I found only 92 hits on the term nutrigenomics in PubMed.

What may we conclude from this quick scan? Although sex related issues are certainly being researched, it does not appear that sex/gender form a clear perspective to study issues that matter in nutrigenomics research. If this were the case, questions that are relevant to women's lives would be subject to research, for example:

- What interactions between nutrition and the menstrual cycle play a role in health and disease?
- Since many chronic diseases in women occur after menopause, how do sex hormones interact in the relationships between nutrition and disease susceptibility?
- What effects do dietary habits have on the development of osteoporosis in women and which role do genetic factors play?
- What is the role of nutrition in diseases with a genetic component that frequently occur in women, for example migraine, depression or asthma?
- How does nutrition interact with genes in the development of eating disorders that occur frequently in girls and women, for example anorexia nervosa?
- What is the genetic basis for low levels of folic acid in women who therefore have a high risk for conceiving children with neurological malformations?

Developing nutrigenomics research from a women's perspective implies that relevant animal models need to be available. I asked one of the leading researchers from the Dutch Nutrigenomics Consortium about this matter. It appears that almost exclusively male mice are being used in animal models and very little is known about the female mouse. We may conclude that much research efforts are needed to develop animal models in order to provide the basis for research in female humans.

One of the perceived applications of nutrigenomics research is the development of individualised diets. We need to realise that the term "individualised" refers to new ways of constructing groups or populations. In the genomics era, specific genetic profiles will be used to characterise populations, in contrast to present practices that use physiological or clinical parameters. In order to prevent the usual gender bias in the construction of populations for the application of nutrigenomics research, social scientists will need to be involved at all stages in research and development processes.

A last comment concerns the larger context of nutrigenomics research. Ordovas highlights two important research areas of nutrigenomics, i.e. cardiovascular diseases and obesity. These diseases are considered to be lifestyle diseases, at least in part. For prevention or treatment strategies we therefore need to consider our lifestyles in addition to the individual susceptibility for disease development. Dietary habits and exercise patterns develop in socio-economic contexts. The interplay between individual behaviour, disease susceptibility and environmental factors, drive the obesity epidemic. Although technological strategies, for example as the result of nutrigenomics research, may help to counter cardiovascular disease and obesity, they stress the individual perspective and responsibilities. Therefore, such strategies may distract attention from the underlying social processes that play a role in the development of cardiovascular diseases and obesity. We need to balance research efforts into nutrigenomics with other types of research, including social sciences, in order to turn the current epidemiological trends.

In conclusion, nutrigenomics is a research area with potentially a large impact on our society. Because research develops as the result of social and economic processes, we need to be aware of the various forms of bias that play a role. Diversity issues need to be considered in this respect.

Discussion

What is the state of the art as regards integration of attention to sex and gender issues in the methodologies of basic and translational research?

Nutrigenomics, a young field of research, tackles the problem from a different perspective. Sex matters. Nutrigenomics deals with complicated and complementary research questions regarding interaction between diet, sex differences and disease.

Population mean differs from the individual. "We are giving advice to people who don't exist" (ie the statistically average person). "One size does not fit all". Individuality needs to be taken into account in health research. There is great variability in diet response. "People respond differently to dietary recommendations".

The research Ordovas reported was done with sex-disaggregated data. Pooling data may have left questions unanswered. The research model was complicated as well. Stratification and focusing on the individual versus studying (sub) populations is an issue. In the methodology of gender research men and women are

split in different cohorts. The results Dr. Ordovas presented, have shown that the difference between men and women is not so much a matter of occurrence, but that the reaction to environmental factors was a determinant worth considering.

Animal models are used to study the biomedical aspects but the role of polymorphisms in humans cannot easily be derived from these animal models.

What are sex and gender differences within nutrigenomics and what are the consequences for diagnostic, preventive and therapeutic interventions?

“Genes have sex: they respond differently”; the effect of certain polymorphisms is apparent only in women. “Men and women respond differently to, for instance, diet. They come with a confusing landscape of health effects. Genes have gender”. “Polymorphisms may be important, but they come with different effects in men and women”.

Also sex-specific responses to pharmaceutical treatments are noted. The effect of polymorphisms depends on what you eat. This effect was only present in women, not in men. “Do men and women respond to diet differently? We do not know for sure”. Controversial findings are for instance that women respond less to diet prescriptions suggesting a gene-diet interaction. The interaction between gene variants and dietary response was seen originally for the APOE gene, one of its common polymorphisms, known as APOE4, is a marker for high cholesterol and men carrying this APOE variant respond to a low fat diet with greater reduction in plasma cholesterol, but this effect is not observed in women. More recently, studies carried out in Spain, the USA and Singapore show that polymorphisms at the Perilipin gene predict risk of obesity in women but not so in men. Moreover, this gene also predicts the response to weight-reduction therapies.

NW: As far as I know, the research that Ordovas is referring to, deals with fat metabolism. Since diets contain many other micro- and macro nutrients as well, I think it is important to restrict the above general remarks to the fatty components in diets. Maybe it is better to make a general statement that, at present, most of the research on nutrigenomics – diet interactions concern fat metabolism, not so much other nutrients.

There is a menstrual cycle - nutrition interaction, which needs to be studied, as well as the relationship of menopause and chronic diseases. Dietary habits, and disorders like anorexia, which previously were only studied among women, need more attention.

What are the conceptual and theoretical challenges?

“Speaking of genes: are we talking about sex or gender?” “The genes play a role, but the environment is important too”. “We were ignoring that diet, activation and environment are just as important”. “Genes have sex: they respond differently”.

The reviewer did a quick search on PubMed using keywords ‘nutrigenomics’ and ‘gender or sex’ but there were no hits. Only 5 reviews on women were available on PubMed. “To this point, PubMed is like the yellow pages without the right term, you cannot find anything”. The major problem is that there is no defined entry for “nutrigenomics” in PubMed. Therefore, by doing a search using this keyword, one will miss most of the relevant articles dealing with gene and diet interactions. Specific nutrigenomics data bases need to be constructed to access relevant information from the published literature.

There is an interaction of genes, sex, gender, lifestyle and environment. Research shows biomedical and socio-cultural causes. Molecular nutrition science or nutrigenomics clusters people or populations, it is a new way of constructing populations statistically, with suggestions for gendered research.

However, we need to look at individuals as well. Individual diets and the interactions with genes are crucial. Predisposition and supplementation cancel one another out. We need to look out how we implement personalized diets. It can be very dangerous to base our diets on population averages. We should take gendered individuals as a focus, not whether someone is male or female.

Complementary research questions are necessary:

- How can nutrigenomics be applied in lifestyle diseases?
- Focus on biomedical and socio-cultural aspects of these lifestyle diseases
- What about risk from accumulating lifetime exposure to certain determinants?
- Pregnancy related diet: did you find out what the appropriate diet is for pregnant women?

“Very little is known about the female mouse”. We know menopause and sex-hormones are very important. Time prior to menopause is important. Health risks accumulate over many years. The influence of folic acid has been studied extensively in foetuses and aging individuals, but not in adults. Socio-cultural factors are major missing variables. To rightfully study gender, research should be multidisciplinary.

An example is the Diogenes project with 3 arms: diet, obesity and genetics using epidemiological cohort studies and clinical trials.

What are the ethical and financial difficulties concerning integration of sex and gender in biomedical and health related research?

In this study “we try to bring together nutrigenomics, diet, trials, clinical research and epidemiology. We do not only want to look at the health but also at the practical parts, application”.

The pharmaceutical industry is harder to work with than the food industry (think about euros and dollars). Food technology should be involved in research and funding of research. “Gender is not considered in the project Diogenes officially. It is sometimes ignored because it’s just there”.

Summary of main discussion points

- Interaction of genes, sex, gender, lifestyle, environment.
- Sex and gender issues in research methodologies.
- Complementary research questions.
- Stratification and the individual vs. (sub)population.

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