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Review

Gender perspectives in European research

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ABSTRACT

Background: Attention to sex and gender aspects in biomedical and health-related research has been a major initiative of the EU gender equality policy for research. The EU funded GenderBasic project (2005–2008), conceived to stimulate this attention to sex and gender and to provide practical tools to researchers, resulted in the publication of 10 reviews by high-level scientists in a Supplement to Gender Medicine in December 2007: "Bringing Gender Expertise to Biomedical and Health-Related Research".

Methods: Four commissioned reviews covered methodological aspects of addressing sex and gender in biomedical research – ranging from basic, molecular to public health research – next to six reviews that addressed sex and gender aspects relevant to selected health areas: anxiety disorders, asthma, metabolic syndrome, nutrigenomics, osteoporosis and work-related health.

Results: The review articles, that were discussed at an expert meeting, attended – upon invitation – by a mixed audience of basic and clinical researchers, epidemiologists, social scientists and gender researchers, came up with excellent state of the art data, solutions to methodological and conceptual problems, practical tools and interesting questions for further research.

Conclusion: The expert meeting created great enthusiasm among the participants and a real exchange took place among researchers from various backgrounds. Most life sciences researchers were familiar with the concept of sex differences but confessed that the effects of socially constructed gender until now, had received too little attention.

The GenderBasic project yielded three major achievements for European research: (1) it stimulated and promoted research into sex differences; (2) it stimulated research into the workings of gender, illustrated by useful examples in particular in understanding masculinity and its effects on the health of individual men; (3) it highlighted sex-gender interaction and granted gender a prominent place on the research agenda that resulted from GenderBasic. A final conclusion of the project was that it is not differences per se that are interesting but rather how, as a result of the interaction between sex and gender, differences develop.

The European Commission selected the GenderBasic project itself as an excellent example of the positive impacts EU research can achieve and the project will be featured in a catalogue of 6th Framework Success Stories.

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1. Introduction

The European Commission (EC) has adopted Framework Programmes for Research with the aim to finance research that is in line with their policy goals. A long standing policy goal has been to promote gender equality. This policy has become enshrined in consecutive treaties and was for the first time applied to *research* under Framework Programme 5 (FP5) [1] Mainstreaming gender equality in research embraces both the stimulation of the participation of women in research at all levels and the consideration of the gender dimension of the research content.

In 2000–2001 the EC commissioned a series of Gender Impact Assessment (GIA) studies of the specific programmes of FP5. Aim of these studies was the evaluation of the gender dimension in the development, management, and implementation of the Framework Programmes. These studies, which were executed by 7 research teams, investigated the participation of women and analyzed whether the research themes, methods, and issues prioritized in FP5 affect women and men differently. Conclusions and recommendations were intended for the preparation and implementation of the next Framework Programme, FP6.

We ourselves conducted the GIA study of the *Quality of Life and Management of Living Resources* programme that addressed the broad range of life sciences research [2]. An important conclusion was that the term 'gender dimension' for life sciences research should be understood as attention to both biological sex differences and to socio-cultural gender effects when relevant. The study has had a big impact. Its recommendations were firmly implemented in FP6 (2002–2006). New guidelines were introduced for applicants submitting proposals in thematic priority 1.1.1. *Life sciences, genomics and biotechnology for health* but were also relevant to thematic priority 1.1.5 *Food Quality and Safety*.¹ Applicants had

to answer a set of specific questions as regards integration of the *gender dimension*.² Integrated Projects and Networks of Excellence also had to write a Gender Action Plan [3,4].

2. GenderBasic project

Biological and socio-cultural differences between women and men may result in different epidemiological patterns and effect modification of diagnostic, preventive and therapeutic interventions. For many researchers integrating a sex and gender dimension in their research presents a new challenge. They furthermore may encounter a variety of conceptual, methodological, practical, ethical and financial problems as they try to integrate sex and gender aspects in their research. Some progress has been made in clinical research in the USA [5,6] However, recommendations made by influential bodies such as the IOM [7,8] and others [9–11] to address potential sex differences in *basic* research have not been widely taken on board. Applying the FP6 guidelines to basic (European) research involving cells, tissues, other materials and animals seems to be confronted with many practical problems and a lack of expertise. Researchers are not unwilling to take sex and gender into account, but they encounter difficulties. Consider a shortlist of problems put forward at a meeting of the Commission Network on Gender Aspects in Food Quality and Safety Research (GENFOOD-SAFE) on Jan 13th, 2004:

'Why is integration of the gender dimension a good thing to do?'

'What is the theoretical basis?'

'We foresee methodological issues (confounding, effect modification)'

'We foresee practical issues (the raising of female rats)'

² Application Form (B 10) questions to answer:
Gender/sex aspects in a proposal if YES to any of the questions:

- Does the project involve human subjects?
- Does the project use human cells / tissues/ other specimens?
- If human subjects are not involved or human materials not used, does the research involve animal subjects or animal tissues (as models of human biology/physiology) in such a way that it is expected that it may have implications for humans?
- Does the project use collection of data related to human subjects, human materials, animal subjects or animal materials?

Are gender/sex differences with respects to the research documented in the literature? YES/NO

- If yes please give details.
- A negative answer to this question may imply some innovation in the proposal towards this issue that will be taken into account in the evaluation process.

¹ The rationale was given in a footnote to the FP6 work programme: *Risk factors, biological mechanisms, clinical manifestation, causes, consequences of disease and disorders may differ in men and women. In such cases, diagnosis, prevention, treatment, and management need to be adapted according to sex and gender. Consequences for not doing so impinge on the health of both women and men.*

In the FP7 work programme for Theme I Health (p. 8) it said:

The pursuit of scientific knowledge and its technical application towards society requires the talent, perspectives and insight that can only be assured by increasing diversity in the workforce. Therefore a balanced representation of women and men at all levels of research projects is encouraged

Gender aspects in research have a particular relevance to this Theme as risk factors, biological mechanisms, causes, clinical manifestation, consequences and treatment of disease and disorders often differ between men and women. The possibility of gender/sex differences must therefore be considered in all areas of health research where appropriate.

'How about financing larger studies?'
 'What are the ethical problems? (more persons exposed to testing)'
 'Jokes were launched ridiculing the gender issue: 'what is the sex of your cells today?'

Apparently, a translation of the guidelines to the level of actual research practices was needed. As we had been involved in drawing up the recommendations, we were now challenged to answer the FP6 call concerning the development of *tools* for integration of the gender dimension in life sciences research. Thus, the GenderBasic project was conceived that ran from October 2005 to January 2008. Its main objective was to provide scientists involved in health-related research (with a focus on basic and clinical research) funded by the EU Framework Programmes with practical tools, relevant examples, and best practices regarding sex and gender differences in the content of their research.

The project consisted of the following activities:

- An assessment of facilitating and inhibiting factors for the incorporation of attention to sex differences and/or gender effects in basic and clinical research among selected FP6 life sciences research projects.
- An assessment of facilitating and inhibiting factors for the incorporation of attention to sex differences and/or gender effects in basic and clinical research among research coordinators of acclaimed European Research Institutes in the life sciences (e.g., Inserm, Charité, Karolinska).
- The production of topical papers by experts, describing best practices and possible solutions for identified methodological and conceptual issues: (e.g. equitable inclusion men and women, subgroup analyses data, sex-gender interactions).
- A meeting for researchers and experts to discuss proposed solutions on issues regarding the incorporation of attention to sex differences and/or gender effects in the content of basic and clinical research. (January 26–27, 2007).
- The development of tools to advise EU services, researchers and research evaluators on how to improve attention to the gender dimension in basic and clinical research.

In this way GenderBasic aimed to contribute to the development of standards and to improve the quality of research in order to meet the goals set by the EU concerning scientific excellence.

3. The GenderBasic reviews

As part of the GenderBasic project ten reviews were commissioned which together cover various aspects of sex and gender in research as well as six health areas in which attention to sex and gender issues is urgently needed. The methodologic reviews address basic, translational, clinical, and public health research. The identified health areas are anxiety disorders, asthma, metabolic syndrome, nutrigenomics, osteoporosis, and work-related health.

The reviews are meant to provide state-of-the-art information about specific problems and opportunities (challenges) and to propose widely supported solutions for integrating sex and gender. We asked the authors to address the following questions: (1) What is the state of the art in integrating sex and gender issues in the methodologies of basic, translational, clinical, and public health research? (2) What do we know? Which gaps in knowledge can be identified that deserve further research? (3) What is the state of the art in integrating sex and gender aspects in selected health areas identified as being in urgent need of addressing sex and gender factors (anxiety disorders, asthma, the metabolic

syndrome, nutrigenomics, osteoporosis, and work-related health)? (4) What do we know? Which gaps in knowledge can be identified that deserve further research? (5) Which tools are needed to promote better integration of sex and gender aspects among researchers?

The reviews were prepared in the second half of 2006 by identified expert authors. High level experts were invited to write critical comments about each review. In January 2007, at an Expert Meeting in Maastricht, the review papers were refereed by the invited experts and discussed by the audience. A report on the discussions and the full text of the comments can be found in the Proceedings, which are available at www.genderbasic.nl/expert_meeting.

The Expert Meeting hosted scientists from a wide range of backgrounds because we intended to cover reviews ranging from molecular research on gene polymorphisms to the effects of health promotion in public health. Basic researchers, clinical researchers, epidemiologists, social scientists, and gender researchers all have different historic positions regarding sex and gender issues. It was necessary to make a clear conceptual distinction between biological sex and socio-cultural gender to avoid misunderstandings. What connected us was a passion to innovate health and biomedical research so that the needs of men and women are met in an equitable way.

4. Results from the reviews and expert meeting discussion

4.1. Levels in research

As stated we promoted a conceptual distinction between sex and gender. However the focus in the GenderBasic project is on *interaction* of sex and gender at all *levels*, from the subcellular (molecular/genetic) to the societal (population). Depending on the level studied, sex and/or gender aspects might be involved. At the *basic/molecular, cellular and organ* level we are dealing with a biological environment that concerns sex related interactions. Examples are gene-gene interactions, sex specific gene expression/polymorphisms, cellular processes, organ (specific) processes, sex hormone dependent receptors, systemic processes.

At the level of an *organism* we are dealing with a biological and social environment that concerns sex related and social interactions. For example: environmental influences (physical), between animal influences (physiological, cycle synchronization), influences between animal and person handling the animal.

At the *human* level we speak about biological and socio-cultural influences that concern sex differences and gender effects. Research involving humans concerns the interaction between possible sex differences and gender *and* other dimensions of difference (age, ethnic origin, socio-economic status, sexual orientation, (dis)ability) as well.

4.2. On methodologies

Research into health and disease benefits from different methodological approaches and researchers work in a variety of epistemological traditions. It will result in a highly pluralistic evidence base. This applies to the contents of the GenderBasic reviews as well. Where randomized controlled trials are the standard in *clinical* research [12], in the context of *public health*, research methods with a gender perspective 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, other forms of literature reviews, meta analysis, accounts of lay or tacit knowledge [13,14] Because gender is a social-cultural-political concept that addresses socio-cultural

aspects, the socio-cultural sciences are needed for health related research. The message could be: stick to your field, but work in multidisciplinary teams.

4.3. On measuring gender

It appeared that the concept of gender still is a difficult one for life sciences researchers. That is not surprising as the concept was launched by the social sciences in the second half of the 20th century. Although a lot of 'missionary work' (see letter to the editor *BMJ*, September 2001 [15]) has been done to define the concept and to distinguish it from sex, a lot of confusion still prevails. Medical discourse tends to address differences between women and men as 'gender differences', sometimes denoting sex differences only. Perhaps this has to do with a resistance felt towards using the term sex differences for humans. On the other hand gender studies research in the non-biomedical disciplines has emphasized the dynamic aspects of the interaction between sex and gender and sometimes is resistant to make a distinction. As we have argued in other places [2,FP5 Gender Impact Assessment study] for the implementation of attention to sex differences and gender effects in biomedical and health related research, we adhere to the distinction for strategic reasons while acknowledging the interaction. For various experts in the GenderBasic expert meeting, the concept of gender *and* the distinction from sex, served as an eye-opener and triggered new research questions.

Resulting views from the expert meeting were:

- Gender cannot be treated as a variable [16]. It is always in the making.
- At present there is no means to measure gender.
- 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 [17].
- More insight into the workings of gender at the individual level (gender role behaviour) was called for (research on asthma, osteoporosis, food allergy, anxiety disorders, and work-related health).

4.4. On measuring sex

- We cannot randomize based on sex [12]. Therefore the best solution is to test the two populations (men and women) separately [12,18]. This suggestion goes well beyond a recommendation to provide sex disaggregated data.
- Practical issues concern power issues, number of respondents involved and recruitment: usually only 30% women become enrolled in clinical trials, where the design would need 50%.
- It was suggested to re-analyze data on sex differences with a gender perspective. This represents an enormous potential of new data.

4.5. On social and ethical issues

- There is a need for establishing good practices regarding integration of sex and gender at laboratory level including normative issues ('good sex and gender practice': GS&GP).
- GS&GP is more expensive (see formula in [12]). Involved is a political decision on how to spend public money.
- More animals are needed if we want to take the female cycle into account (stratified research) [19]. This could create tensions with the EU rules on animal welfare (3R's: reduction, replacement, refinement).
- Obviously GS&GP involves ethical issues. A point raised by the Commission represented by Mary Fitzgerald, was to stimulate including gender issues in the Ethical Review.

4.6. Research & funding by pharmaceutical firms

Pharmaceutical firms go for maximal profits. The pharmaceutical industry seems reluctant to fund sex based research. Experts at the meeting phrased it as follows: "Firm Z turned down all data directed at sex differences for their metabolic syndrome drugs" and "Pharmaceutical companies do not set out to study differences between males and females because it might affect incomes". They are not interested in paying for stratified research. A strategic approach, mentioned by another expert was: "to fiddle sex and gender into design", i.e. not naming stratification on application for funding but in the end stratify anyway.

Could the food industry be considered an ally in nutrigenomics?

5. Summary of disease related reviews and expert discussion

The 10 reviews have been published in the journal *Gender Medicine* in December 2007 [20]. In this section a summary of salient findings is given of the reviews on asthma, osteoporosis, metabolic syndrome and nutrigenomics. No summary is included of the reviews on anxiety disorders [21] and work-related health [16] as these reviews covered no pharmacological aspects.

5.1. On asthma [18]

Asthma prevalence is higher in boys before puberty and in women in adulthood.

There exists a possible under diagnosis in girls (Yentl effect), especially in low-income groups. The Yentl syndrome refers to the fact that a woman has to masquerade as a man in order to receive the same treatment.

The role of gender is visible in parental reporting about symptoms of their sons and daughters (more reporting in boys); more boys receive treatment. Consequences of this bias affect recruitment and clinical data (see also [22]).

Severe asthma is more predominant in women; it has to be established whether this is a social, cultural, hormonal and /or genetic issue.

There is bias in diagnosis by physicians: adult women are diagnosed with asthma, men with COPD.

Sex differences in the development of the pulmonary system are visible in utero. Girls have relatively larger airways in proportion to lung volume than boys.

Hormonal changes and genetic susceptibility are likely to contribute to the change in prevalence around puberty.

The relative contribution of genetic disposition, hormonal influences and social environment (gender role behaviour) is under researched (breastfeeding boys/vs girls, smoking behaviour mother/father, type of cooking, house mite reduction).

Gender role behaviour: Peer pressure on boys to hide their asthma (and allergy) from peers and not using inhalants when in company has been documented. Girls incorporate their asthma in their social circle. Gender identity and socialization are thus important in therapy compliance.

Men and women may respond differently to treatments due to biological, environmental and social influences

5.2. On osteoporosis [23]

The incidence of fractures is higher in boys than in girls

The burden of fractures increases with age and is higher in women

With increasing life expectancy we will be confronted with increased mortality (more in men), increased morbidity (same in men and women) and high costs (more in women)

The difference in incidence is related to factors that determine fracture risk: there are factors related to bone and related to falls.

Risk factors are different for men and women.

Causes of falls should be explained by both different levels of activity (related to gender role) as well as differences in muscle control (biological difference; oestrogen effect on muscle tissue)

Women are the focus in research on osteoporosis and serve as standard for men.

Drugs are tested on women and prescribed to men [24].

Over exercise and dietary restrictions are detrimental for women and men. Running marathons is unhealthy especially for men.

Next to the biological factors there is a need to take into account co-morbidity, life style factors and social support from a gender perspective.

Osteoporosis is a clear example of candidacy [24]. Candidacy refers to the neglect of the other sex if a condition is labeled as 'female' or 'male' disease.

5.3. On metabolic syndrome (MetS) [25]

The prevalence of MetS that used to be higher in men has increased considerably in young women driven by obesity.

Women check their weight regularly, men don't, and their overweight is not picked up.

Men are under diagnosed, despite the same symptoms; the prognosis on the long run is worse in men.

Diagnostic criteria for the MetS vary for the cut-off points and definition of its components in sex specific ways (resulting in epidemiological differences).

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.

The risk factor hypertension rises steeper in aging women than in men.

Hypertension and diabetes (as components of the MetS) carry a greater risk for cardiovascular disease in women.

Visceral 'male' fat seems to be a source of inflammatory mediators; subcutaneous 'female' fat seems to be protective.

Criteria for risk management in MetS patients should take account of sex and gender.

The importance of changes in life style was emphasized such as a Mediterranean diet and exercise for women.

"We know so much but do so little" (comment made by Swahn at the meeting).

5.4. On nutrigenomics [26]

Nutrigenomics is a research field aimed at the health of the entire population.

The focus is on interplay between genes (genetic polymorphisms in the context of sex) and disease susceptibility. Additional complexity is brought up by dietary habits and environment (gender roles) in the modulation of the balance between health and disease.

This complexity underlies the poor replication obtained for most candidate gene association studies examining common diseases and their predisposing factors.

Research data from two important research areas in nutrigenomics i.e. cardiovascular diseases and obesity, illustrate the interplay between genes, disease susceptibility, dietary habits and the relevance of sex differences.

Research data on polymorphisms of APOE (involved in lipid metabolism and risk for CVD) and PLIN (involved in obesity risk) support the role of sex specific polymorphisms in the differential response to the environment; differences between men and women and differences within women were demonstrated.

"Genes have a sex: they respond differently; the effect of certain polymorphisms is apparent only in women".

Important aspects that need to be studied are: Risk from accumulating life time exposure to certain determinants, menstrual cycle nutrition interaction, pregnancy related diets, menopause. These aspects are absent from mouse models.

6. Expected impact: new perspectives and paradigms

Peer review and discussions at the meeting proposed new avenues for research of which we highlight those for *animal research* concerning strategies to detect small differences and for research into *life style diseases* (obesity and metabolic syndrome) as paradigmatic for the interaction of sex and gender.

6.1. Animal models [19]

Very small differences between the sexes produce clinical treatment effects because small differences may have additive/synergistic effects and therefore have to be investigated. Current obstacles to discover small differences are:

- Sex hormones, level of estrogens and the menstrual cycle are complex to consider, yet may be active in multiple ways.
- Oestrogen effects are leveled out due to variability (in cycle) among females (statistical mean). Effects are lost.
- Research hardly considers the importance of progesterone, or other neurosteroids that vary during the oestrus cycle. Levels of testosterone are not measured.

Holdcroft stated that animal models are needed that are adequate for studying human disease; current ones cannot consider comorbidity, age related changes, cycle changes, use of contraceptives. Her recommendations:

- For male and female animals, their age and weight should be recorded and for females, their reproductive status and ovarian cycle phase should be determined as accurately as possible.
- The sex of origin of biological research materials should be determined and disclosed on publication.
- In study design, reporting and peer review, the possible variations and impact of sex differences on all aspects of the experiment should be considered and be based on evidence relevant to the strain, species and environmental conditions.

In her comments Flavia Franconi ([27], see also [28,29]) pointed to sex dependent programming. She further emphasized the following issues:

- Social interactions and environment are relevant for laboratory animals and thus may have important consequences in preclinical research.
- Early life social interactions and environment should be emphasized; diet, mother-pup interaction and neonatal handling affect males and females differently.
- Attention is needed to non hormonal events, such as expression of sex chromosome genes.

- Life experiences (pregnancy, lactation) should be studied in pharmacological research.
- The scenario of activity of sex hormones is very complex depending on receptor subtypes, tissue co-activators and repressors.
- An animal model is needed that is similar to humans and includes oral contraceptive use.
- Understudied is whether males and females respond differently to placebo administration. This is also relevant to animal research and concerns vehicle use and sham operations.

6.2. Life style diseases

Life style diseases are paradigmatic for the interaction between sex and gender (and other dimensions of difference). To address life style diseases a focus on both biomedical and socio-cultural aspects is necessary. Research questions are best studied in multidisciplinary teams. Two reviews explicitly addressed life style diseases i.e. obesitas and metabolic syndrome. Ordovas [26] pointed to differences between countries, candidacy and sex differences. Regitz-Zagrosek et al. [25] stated that metabolic syndrome is difficult to assess: biological, genetic dispositions interact with life style factors; this is a plea for analysis from a life time perspective.

To adequately study not only the interaction between sex and gender but also between other dimensions of difference an *intersectional* approach was advocated: keep the panoramic view, combine the genome-proteome-environment in studying sex & gender (and other dimensions of difference) [26,30–32].

7. Research priorities building blocks for a research agenda

Explicit assignment for the authors and peer reviewers was to propose new research questions based on their reviewing of the state of the art. Their ideas in fact constitute building blocks for a future research agenda that that should be incorporated in updates of the FP7 work programme [33].

8. Discussion

In FP6, guidelines for integrating gender equality in life sciences research have been introduced as a top down instrument. These guidelines were relatively new especially for researchers in basic research. Real awareness of sex and gender aspects in *basic* research and integration of the gender dimension in research practices is not yet developed. Integration of the gender dimension in basic research can be seen as an innovative change of current research practices. Such a change can only be accomplished if the researchers involved, view this change as necessary, feasible and contributing to the quality of their research. A careful dialogue with the target group, i.e. the researchers and experts, seemed crucial. That is why the GenderBasic project commissioned the reviews from the scientific community itself. It was expected that in this way evolving tools and recommendations, as input from actual research practices, would have a broad support.

In sum: The GenderBasic project promoted balanced, justified attention to both sex differences and gender effects, and proposed an agenda for future research [34]. Differences of both kinds are interesting and relevant, and are best studied in multidisciplinary teams. The most interesting areas of study are not the differences per se, but studies on how differences develop (see also [35–39]). The new perspectives and models developed through the GenderBasic project concretise this view and are helpful in realizing and executing the resulting research agenda.

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