The contribution of sex and gender analysis to research

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Educational aims

- To encourage analysis sex and gender in biomedical research
- To highlight the need of biomedical researchers for practical tools in sex and gender analysis, such as those provided by the Gendered Innovations Project
- To emphasise that integrating sex and gender analysis (together with intersecting factors) provides excellence in research and sparks new knowledge

Key words
Sex, gender, research, gender medicine, gendered innovations project

Abstract

This brief paper highlights the EU/US Gendered Innovations (GI) Project which aims to develop methods of sex and gender analysis for research. A total of 21 case studies from a broad range of scientific fields offer concrete illustrations of how sex and gender analysis leads to new ideas and excellence in research . Two case studies are described to some extent: stem cell research and an example on the increase in non-communicable diseases from the field of nutrigenomics. The peer-reviewed full case studies, including all references can be found at the GI website. In Horizon 2020 "*Gender will be addressed as a cross-cutting issue in order to rectify imbalances between women and men, and to integrate a gender dimension in research and innovation programming and content*". Applicants are referred to the GI materials as a resource for those topics flagged for gender relevance.

Introduction

Research addressing sex and gender in biomedical sciences and clinical medicine is emerging as a promising field. 'Gender Medicine' (GM) is increasing the evidence on differences between women and men in pathophysiology and manifestation of many diseases and in received health care. There is an increasing recognition that both sex and gender affect the health of women and men. Sex refers to biological differences between women and men: genetic predisposition to diseases, body size and composition, drug metabolism. Gender refers to cultural and social attitudes that together shape "feminine" and "masculine" behaviour. Humans function in large and complex societies through learned behaviours. Gender is one aspect of these sets of behaviours and therefore gender based attitudes influence health. GM duly recognizes that sex and gender (S&G) influence each other and are inseparable in their relation to human diseases. Shorter life span and myocardial infarctions at younger age in men may be due to biological causes, such as a recently discovered gene variant on the Y-chromosome, but may also be related to stress or risk taking behaviours. Vice versa, gender based life style factors, smoking, toxins, nutrition and exercise modify DNA packaging and gene transcription by epigenetic mechanisms and thereby alter body composition. Adverse drug effects cause a large number of medical complications particularly in women which may be due to sex differences in drug metabolism as well as to gender related differences in prescription and drug use. Interaction of sex and gender related mechanisms leads to different manifestation of frequent diseases such as infarction, heart failure, diabetes, rheumatic disease and also infections in women and men.[1-6]

Innovations through gender

Given the wealth of evidence as described above it has become a matter of urgency to provide the research community with appropriate tools to address sex and gender in their research. In 2011 the European Commission established the expert group 'Innovation through Gender' directed by Londa Schiebinger and Ineke Klinge to develop the much needed materials. A Gendered Innovations website had already been started at Stanford University by Londa Schiebinger in 2009. The initiated EU/US project Gendered Innovations in Science, Health & Medicine, Engineering and Environment can be seen as following up on earlier EU framework projects addressing the gender dimension of the

research content, representing a translation of the EU gender mainstreaming policy to research policy.[7,8]

Identifying gender bias and understanding how it operates in science and technology is important. But analysis cannot stop there: designing sex and gender analysis into research stimulates new knowledge and technologies. From the start, sex and gender analyses act as additional "controls" (or filters for bias) to provide excellence in science, health and medicine, and engineering research, policy, and practice.[9]

Gendered Innovations 2011-2013

To achieve these goals, the Gendered Innovations (GI) 2011-2013 project aimed at providing researchers with the tools to integrate sex and gender analysis in their research design. In seven international collaborative workshops, held in Europe and the US, materials have been developed and peer reviewed by 57 experts from different scientific fields (see contributors on the website) together with gender experts. The website portals contain the following materials:

- *Methods* of sex and gender analysis relevant to science, health & medicine, engineering and environment
- *Terminology* defining key concepts used throughout the site;
- *Case Studies* documenting specific gendered innovations and demonstrating how methods of sex and gender analysis are applied in specific examples.
- The final report *Gendered Innovations. How gender analysis contributes to research* was presented in a special session in the European Parliament in July 2013 together with the final smart website available at: http://ec.europa.eu/research/science-society/gendered-innovations/index_en.cfm.[10]

On adopting the Horizon 2020 programme for research and innovation the EC has formulated an important article (#15) in which it reaffirms its commitment to integrate sex and gender analysis into research.[11] Applicants for projects under Horizon 2020 are directed to the GI website materials when a particular topic across various fields has been 'flagged' to consider the relevance of incorporating a sex and gender analysis.

GI narratives

The two GI narratives below are an illustration of the new knowledge that can be created by integrating a sex and gender analysis.

Stem cell research

Between 1997 and 2000 ten drugs were withdrawn from the U.S. market because of life-threatening health effects; eight of these posed greater threats for women. Not only did these drugs cost billions of Euros to develop - but when they failed, they caused death and human suffering. There are many reasons why drugs fail - and they fail more often for women.

Most research is done in males, whether human or animal, and the sex of cells and tissues is often not taken into account. [12,13] This has serious implications. for example, in stem cell research, a highly valued area of research. Stem cell research holds promises for treating debilitating diseases, such as Parkinson's disease and muscular dystrophy. Stem cell research focuses on inducing pluripotency in cells derived from adults and using these cells to repair or reconstruct organs. Yet, in most labs, the sex of the cells is not taken into account, which can lead to life-threatening consequences and leave researchers with unsolved puzzles. Take for example the problems an international collaboration between labs in Norway and Australia encountered working with bone marrow stem cells in mice. Researchers in the labs appropriately used both male and female mice, but they used all female stem cells without considering why. This was an unconscious decision and the result was that their male mice died - and they did not understand why.

Some answers to this problem are given on the Gendered Innovations website - and they are real eye openers: importantly, taking sex into account can advance basic knowledge. Research has documented potential sex differences in the therapeutic capacity (such as proliferation and differentiation) of stem cells as well as sex differences in receptor-mediated pathways. For example: muscle-derived stem cells have the capacity to repair heart muscle tissues as well as skeletal muscle tissues. Researchers found that XX cells, showed a higher regenerative capacity than XY cells. This constitutes an important therapeutic finding. Of course there are other variables besides sex at play, such as the type of stem cell being used, type of disease being treated, and hormonal and environmental factors plus their interactions. But we cannot neglect the sex of cells. So what happened with the Norwegian and Australian labs? Once they considered all combinations of sex in donor/recipient interaction, they had greater success with their experiments. The GI method: *Analyzing Sex* summarizes the important steps - the key message is that researchers report the sex of cells and consider the sex of both the donor and recipient in their research.

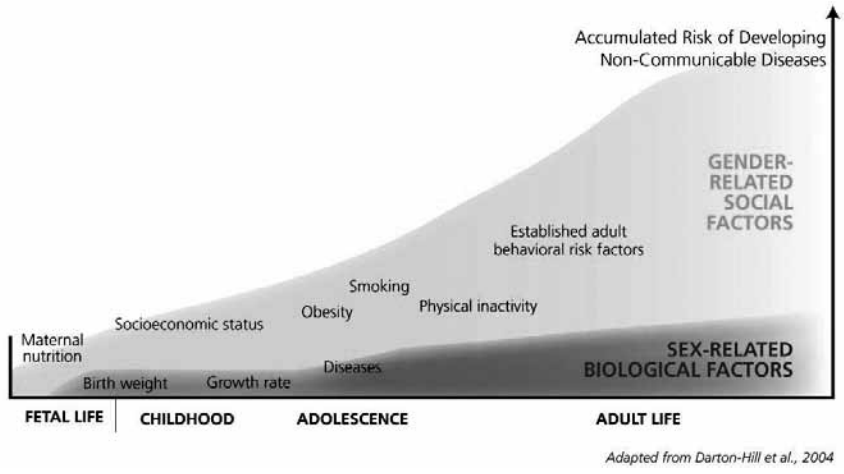
Nutrigenomics

A second story comes from the field of nutrigenomics - an important area for public health - and a priority for Horizon 2020.

The epidemic of non-communicable diseases - heart disease, diabetes and cancers - is on the rise across Europe and North America. These diseases are caused by risk factors such as unhealthy diets, lack of exercise and smoking tobacco, and can be eradicated through smart research and policy. To develop excellent research in this area, we need to understand how sex and gender (plus income and other social factors) influence these risk factors

Fig 1 shows the relative influences of sex- and gender-related factors determining a

Figure 1: Cumulative life course risk factors for non-communicable disease (NCD)
Highlighting the influence of sex and gender-related factors



person's risk for non-communicable diseases over her or his lifetime. Importantly both gender-related social factors and sex-related biological factors interact from the time you are in the womb to determine how well you age. Obesity (a risk factor for diabetes) is an example where gender analysis is important. To understand differences in women's and men's obesity rates, we need to analyse gender differences in lifestyle. Perhaps gender norms in society lead men to exercise more than women; this can lead to greater disease among women. And perhaps gender norms in society lead men to eat less healthy food than women. This gendered behavior can lead to greater disease among men.

So gender behaviors can influence health. And so can biological sex. Analyzing sex is important too in the field of nutrigenomics. Figure 2 shows how gender-related food intake is translated into sex-specific basic metabolism, gene expression, and, finally, into the response to diets. Nutrigenomicists have used sex analysis to explore - at the functional, mechanistic level - how nutrients affect gene expression and cell function in women and men. In one study, they examined vitamin E gene interactions affecting the incidence of respiratory tract infections in the elderly. The main finding suggested that the effect of vitamin E depended on sex: only in women - with a certain genotype - did vitamin E reduce respiratory tract infections.

Finally some more examples of Gendered Innovations in summary:

1. Sex analysis has revealed that the pathophysiology of CVD is different in men and women especially in younger women. It has led to better diagnostic techniques and symptomatology. Analyzing gender assumptions has improved the understanding of risk factors and prevention.
2. The inclusion of men in osteoporosis research has led to better diagnoses and treatments. In the past, osteoporosis was conceptualized as a disease of postmenopausal women.
3. Sex analysis in animal research has led to new knowledge about how sex hormones influence basic molecular pathways involved in immune system function.[14]

Key points

By employing sex and gender analysis as a resource to create new knowledge and technology researchers can:

- add value to research and engineering by ensuring excellence in outcomes
- add value to society by making research more responsible to social needs
- add value to business by developing new ideas, patents and technology.

Conclusion

Integrating sex and gender analysis into all phases of research has been shown to spark creativity by offering new perspectives, posing new questions and opening new areas to research. Sex and gender analysis enhances excellence in research and will make research responsive to the needs of the whole society, both women and men.

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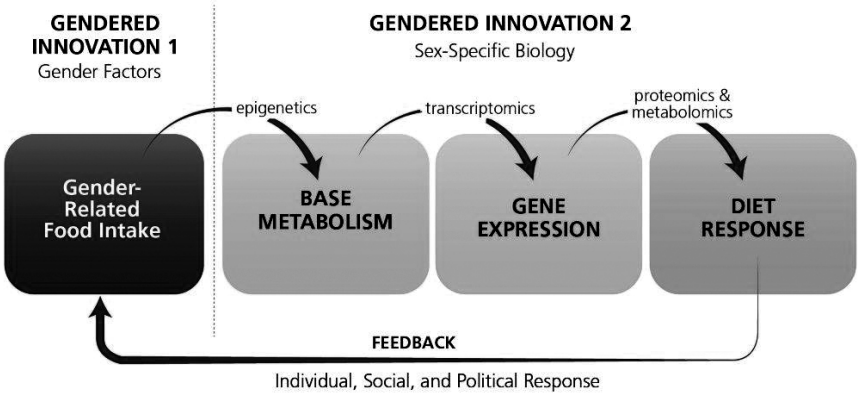
This website is peer-reviewed. All materials were developed in a series of Gendered Innovations Workshops and reviewed by experts (see Contributors).

Further Reading

- Sex and Gender Differences in Pharmacology. Series: Handbook of Experimental Pharmacology, Vol. 214. Regitz-Zagrosek, Vera (Ed.) 2012, IX, 600.

Figure 2: Gendered model for analyzing mechanisms involved in food intake and processing



The diagram above illustrates how researchers might analyze a three-way interaction between gender-related factors, sex-specific biology, and various biological mechanisms involved in human food intake and processing. Gender-related food intake is translated into different sex-specific base metabolisms, gene expressions, and dietary responses, thereby making nutrigenomics a pervasive Gendered Innovation. As such, it exemplifies the relationship between the Gendered Innovation (GI1) discussed above and Gendered Innovations 2a, 2b, and 2c discussed below.