



European Gender Medicine Network

Charité - Universitätsmedizin Berlin, Germany (Coordinator)

Maastricht University, Maastricht, the Netherlands

European Institute of Women's Health, Dublin, Ireland

Report from the Kick-off conference

Brussels, April 7th, 2014



EUGenMed Aims

On April 7th 2014, the European Gender Medicine (EUGenMed) consortium held its kick-off conference. At this meeting with an international and multidisciplinary group of experts and stakeholders, composed of both women and men (see list of participants), a strong consensus was reached about the importance of including sex and gender in European biomedical and health research. Experts and stakeholders are now engaged and ready to proceed with developing a strategy for their further implementation. The goal of EUGenMed is to outline a roadmap for implementing sex and gender in biomedical and health research in Europe, an initiative which is based on good science, improves the quality of healthcare for both women and men, makes European healthcare systems more sustainable and keeps European research on the cutting edge of innovation worldwide.

The Position of the European Commission

Patricia Reilly, member of the Cabinet of Commissioner Geoghegan-Quinn who is in charge of



Patricia Reilly, member of cabinet of the commissioner Máire Geoghegan-Quinn, DG Research, Innovation & Science

Research and Innovation, opened the kick-off conference. Reilly stressed the importance and the strong commitment of the European Commission to research that addresses sex and gender in biomedical sciences and health research. She emphasised that such research is a novel and promising field, but reminded delegates that it is also crucial that EU Member States' national research and innovation programmes take account of the sex and gender dimensions. She expressed the hope that the Horizon 2020 programme would also inspire member states to take measures in this direction. Moreover, she highlighted the importance of involving experts and stakeholders in building strong, sustainable networks. *"We count on all of you to make it happen. The recommendations from EUGenMed will help to further improve the current*

situation in medical research and provide powerful input to European health and research policy, and last but not least, put Europe on the cutting edge of innovation to the benefit of our economy and society at large."

Why It Is Needed to Implement Sex and Gender in Biomedical and Health Research

Excellent science, competitive industry, and tackling societal challenges are central for Europe's Horizon 2020. As it was reinstated and the object of consensus at the EUGenMed kick-off conference, Gender Medicine can contribute to all these goals; it is in fact crucial for their realisation. Outstanding and ethically sound biomedical research, responsible innovation and valuable medical and pharmacological products, a healthy citizenship and efficient and sustainable healthcare cannot be achieved without taking account of sex and gender. The 'one size fits all' model that has informed and dominated medicine until today has to be abandoned in favour of a more targeted approach, one that seriously takes into account the sex- and gender-related dimensions of health and disease. This is critical for the European Union's ambitious target to achieve an increase of two healthy years for Europe's ageing population under the Horizon 2020 programme.

Sex – conventionally understood as biological difference between male and female individuals – and gender, the socio-cultural constructions of and attitudes towards masculinity and femininity – matter in health and disease. Sex – in terms of e.g. hormonal or genetic differences – and gender – in terms of e.g. lifestyle, (risk-taking) behaviour and more generally social and cultural norms – interact to produce different behaviours and health outcomes throughout the life course (see figure 1). Blindness to their relevance and impact can have devastating and sometimes even deadly consequences.

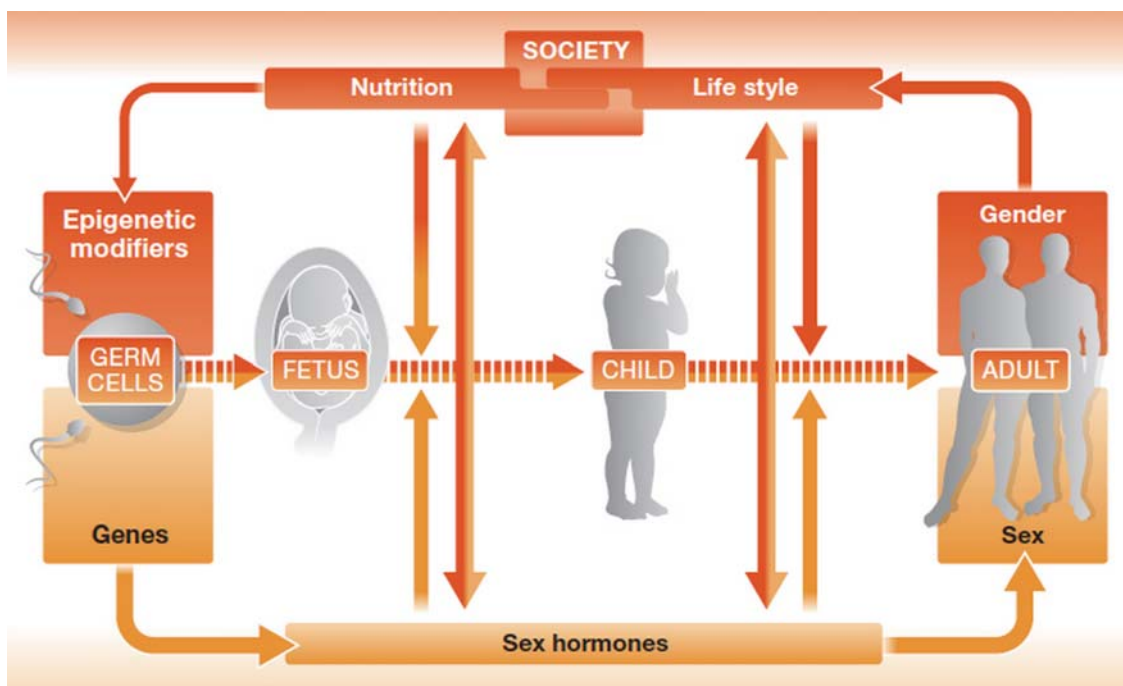


Figure 1. Interdependency of Sex and Gender throughout life (source: Regitz-Zagrosek, V. 2012. Sex and Gender Differences in Health. EMBO Reports 13(7):596-603)

Attention to sex and gender in biomedical and health research is an important quality issue in medicine. As compellingly shown by the participants of the EUGenMed kick-off conference, women and men have different manifestations of disease, pathophysiology, responses to interventions and drug treatment, environmental exposure, awareness of risks, etc. For example, cardiovascular disease is predominantly considered mainly affecting men. In women it remains under-diagnosed, is less aggressively treated or under-treated, despite death from the first myocardial infarction being higher in young women than in men of the same age.

Conversely, women tend to constitute the standard against which men are assessed in osteoporosis, the latter being considered a postmenopausal women's disease even though men after the age of 75 represent a third of osteoporosis-related hip fractures in Europe. Examples such as these of sex and gender differences and their interaction were discussed during the kick-off conference¹.

¹ For more details, please visit the EUGenMed website (<http://eugenmed.eu>) where the individual and overall session reports as well as the kick-off conference's presentation slides can be accessed.

Sex and Gender in Clinical Medicine

In addition to cardiovascular disease and osteoporosis, in the first kick-off session, centred on sex and gender in clinical research and clinical pharmacology, diabetes, chronic kidney disease, gastrointestinal and autoimmune diseases, lung diseases as well as alcohol-related disorders have been identified by the kick-off participants as domains in which sex and gender-differences have been registered. Clinical manifestations and outcomes differ in these diseases among women and men as well as treatments. As shown by the charts below (see figure 2) and that were presented at the kick-off conference, there is a significant imbalance between men and women in organ allocation (in this case kidney and heart transplantation). From the data gathered at the Deutsches Herzzentrum Berlin for instance, it has been established that men receive 82% of organs even though the women presenting at the transplantation centre have a more severe disease. Likewise, living donor kidney transplantations is characterised by a significant imbalance between men and women, especially when one considers spousal donations that are predominantly wife-to-husband (69%).

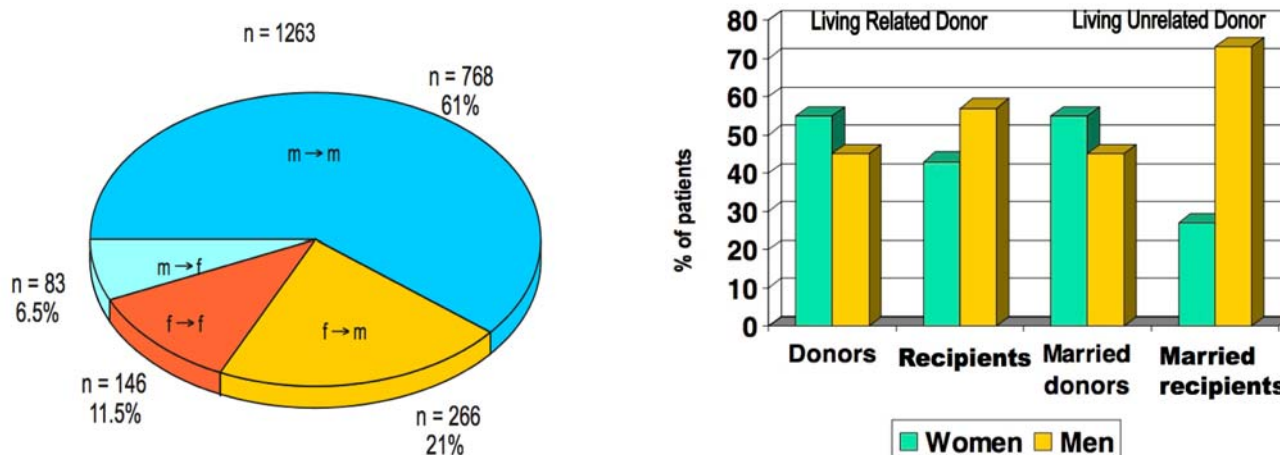


Figure 2. Sex of donors and recipients in heart transplantation (left) and living kidney transplantation (right). Heart transplantations are indicated as donor and recipient sex, e.g. m-m – male to male, f-m – female to male. (Source: left - <http://charite.de/gender>, data from Deutsches Herzzentrum Berlin (DHZB); right – Kyler L et al., *Clinical Transplantation*, 2002, 73:248)

In clinical pharmacology, a greater prevalence of adverse effects in women is well known but the reasons are still not clear. In this respect, between 1997 and 2000, ten drugs were withdrawn from the marketplace in the United States because of adverse and even life-threatening health effects. Eight of these had more serious effects in women. This is in part due to the fact that pre-clinical and clinical drug development does not consider sex differences in a systematic manner. Most drugs are developed in male rodents (see below) and the early clinical studies include more men than women. In clinical drug development, the effects of sex specific body composition (higher percentage of adipose tissue in women), differences in drug resorption and metabolism that might lead to sex specific dosing recommendations are frequently neglected. Furthermore, sex differences in pharmacodynamics are often not specifically addressed in phase II. The phase III clinical studies are still not including adequate numbers of women in some areas, e.g. cardiovascular diseases and they are not aiming at detecting heterogeneity between women and men or analysing sex specific-

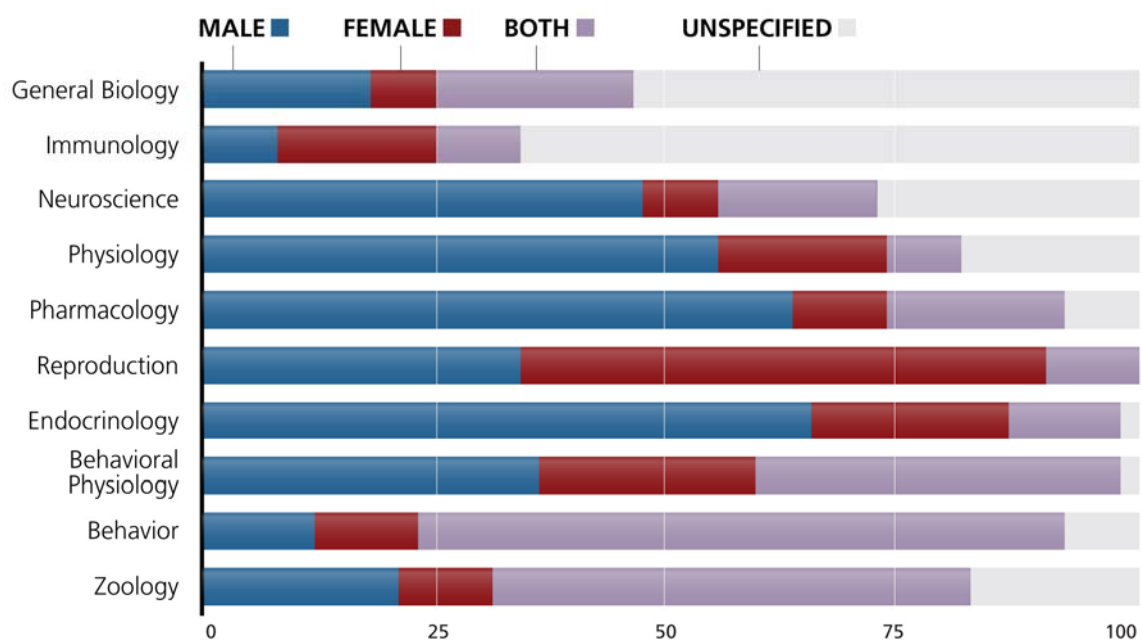
effects. This has led to a portfolio of drugs that are mainly targeted at men and that are not optimized for women. The workshop will analyse how this relates to a higher number of adverse effects and a lower efficacy in women.

Sex and Gender in Basic Biomedical Research and Pre-Clinical Drug Development

Research using animals has been vital to Western science and medicine since its inception. Until the 1960s, however, the sex of animals used in research was rarely reported except in experiments related to reproduction. Even today, the sex of animal subjects is “omitted in 22–42% of articles in neuroscience, physiology, and interdisciplinary biology journals” (Beery et al., 2011). Analysis of animal studies in which sex is reported shows that females are underrepresented in most subfields except reproductive biology and immunology— (see figure 3).

Proportion of Research Studies Using Male and/or Female Animals

From published journal articles within specified biomedical subfield, 2009



Adapted from Beery et al., 2011

Figure 3. Males still dominate animal studies

This slide shows the proportion of research studies, from different biological subfields, that used male (blue), female (red) or both animals (purple) and the proportion that did not give information; the grey bars. Notice the large unspecified part for example for immunological research

In particular, cardiovascular physiology is usually studied in young male mice but hardly ever in females. As a result, some drugs that are effective in males are not effective in females as shown in figure 4, where a transgene developed to protect after myocardial infarction improved survival in the overall group as well as in males but not in females. The big effect in males will hide the lack of effect in females if studies are not designed and analysed to detect a sex difference.

Relatedly, while therapies are developed in males, harmful or protective pathways in females that may also lead to promising drugs, are not analysed.

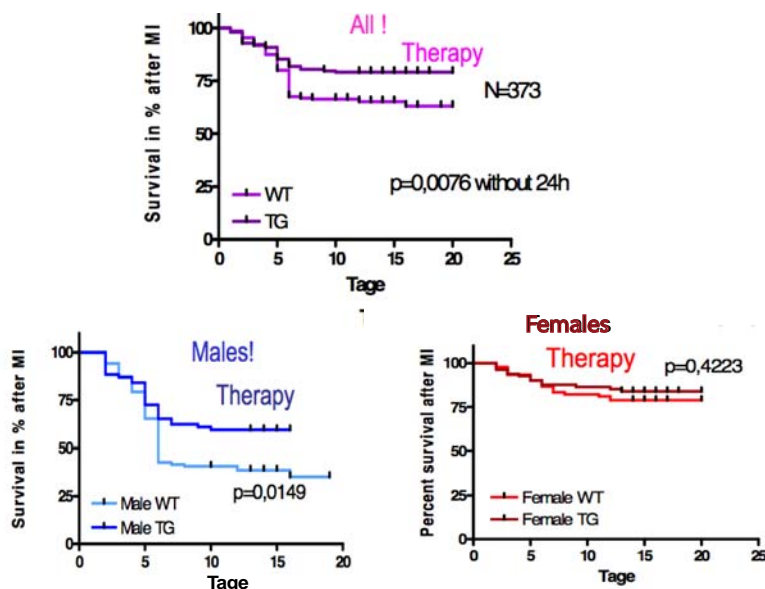


Figure 4. Drug development for myocardial infarction in mice. Survival in the groups with therapy (upper lines) is better than in the untreated groups - in the whole group (upper middle) and in males, but not in the females.

(Source: Unsöld B et al. 2014. Cardiovascular Research 101:97)

Sex and gender also plays a role in the developmental origins of health and disease, now a topic in the new discipline *DOHaD*. The environment of the fetus and of children affects development in a sex specific manner. This is based on sex-specific epigenetic processes that are controlled at the cellular, chromosomal and hormonal level. More concretely, obesity, cardiovascular diseases and diabetes are the product of gene-environment interactions and have their roots in infancy. It is therefore crucial that researchers pay attention to sex and gender in basic biomedical science and pre-clinical drug development.

Sex and Gender in Public Health and Prevention

Sex and gender are also issues of public health and prevention, as discussed by participants in our second session. Cumulative life course risk factors for non-communicable disease (NCD) like

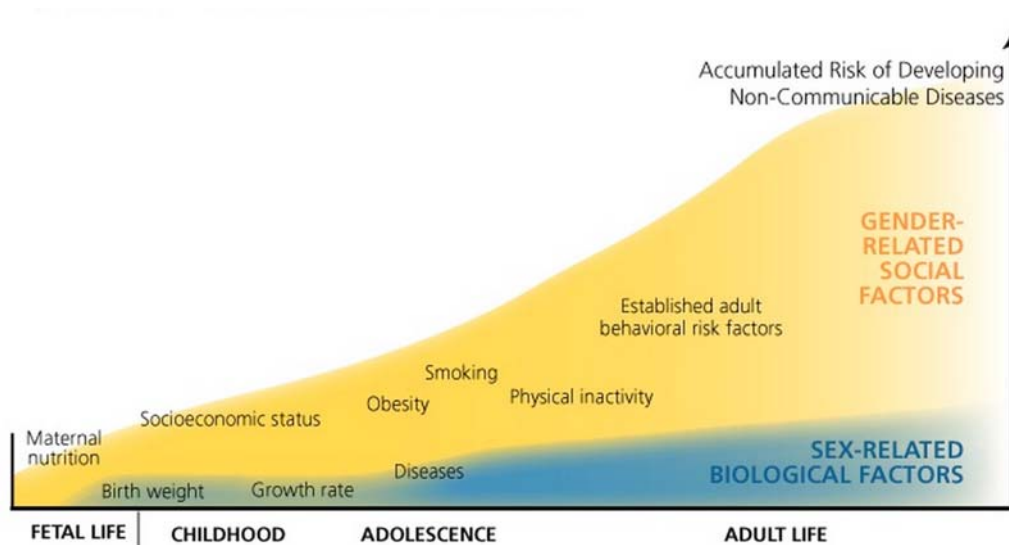


Figure 5. Cumulative Life Course Risk Factors for Non-Communicable Disease

Source: http://ec.europa.eu/research/science-society/gendered-innovations/index_en.cfm

cardiovascular diseases, cancers, chronic respiratory diseases are influenced by sex, gender and their intersecting factors, e.g. socioeconomic status, ethnicity, sexuality or disability (see figure 5).

For instance, to understand differences in women's and men's obesity rates, we need to analyze gender differences in lifestyle. Perhaps gender norms in society lead men to exercise more than women; this can lead to greater disease among women. Or perhaps gender norms in society lead men to eat less healthy food than women. This gendered behavior can lead to greater disease among men.

The experts and stakeholders participating in the EUGenMed's kick-off conference urged that researchers, doctors, teachers and medical students as well as policy makers, funding bodies, regulators – including the European Medicines Agency – and pharmaceutical companies investigate, record and take into account sex differences and effects of gender in various medical conditions and prescription of medication.

Sex and Gender in Medicines' Regulation and Medical Education

As discussed in our fourth session dealing with sex and gender in medicines' regulation and medical education, participants in clinical trials are still predominantly male. As shown in figure 6 below, the percentage of women participating in clinical trials for hypertension (BP), diabetes mellitus (DM), hypercholesterolemia (Chol), with aspirin (Asp), ischaemic heart disease (IHD), heart failure (HF), atrial fibrillation (Afib) and stroke varied between 27.3% (IHD) and 41.4% (DM).

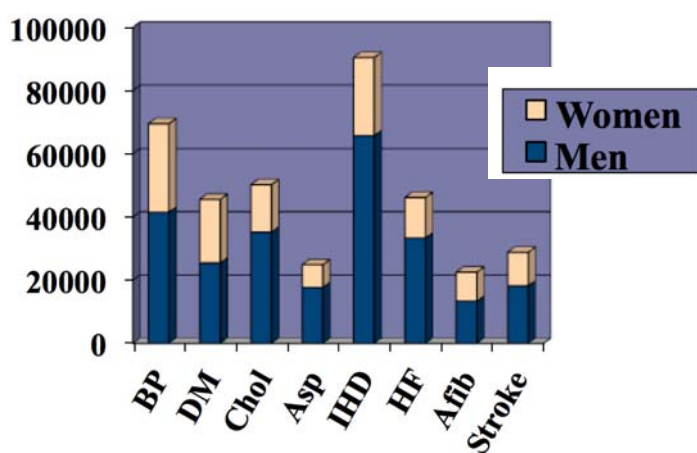


Figure 6. Female and Male Participants in clinical trials for diverse diseases and treatment groups

(Source: Stramba-Badiale, M. 2010. "Women and Research on Cardiovascular Disease in Europe: a report from the European Health Strategy (EuroHeart) Project". *European Heart Journal* 31(14:1677-1687))

It is crucial that preventive and therapeutic interventions be tested in populations that represent the proportion of men and women who suffer from the disease. In this respect, the European Medicines Agency (EMA) will have to look at the new Clinical Trials legislation which asks for an increase in the participation of women and older people in clinical trials. This new Clinical Trials Regulation, will enter into force in 2016 in all EU Member States. It will have to take into account both age and gender of the population to be included in clinical trials. The new legislation will also provide rules for the inclusion of pregnant women under the strictest safety conditions, thus addressing long-standing blind spot in research and clinical trials.

Furthermore, insofar as the way in which tomorrow's physicians are trained will define the quality of health care in the very near future, integrating sex and gender in medical education has to be

made a priority. The 'bikini model' that characterises the inclusion of sex and gender in medical education and focuses mainly on reproductive health is no longer sustainable. The ways in which sex and gender influence the health and well-being of patients must be part of (future) physicians' training. While teaching materials already exist, additional ones will be developed during the EUGenMed's upcoming workshops.

If we are to improve the health of all European citizens and reach the European Union's goal of witnessing an increase of two healthy years for our ageing population by 2020, it is in fact urgent to implement sex and gender in biomedical and health research, including medicines' regulation and medical education, in Europe. It is to achieve this goal that stakeholders' involvement, consensus building and dissemination of the EUGenMed's project findings in a targeted and customised fashion have also been important discussion points at the kick-off conference.

Towards a Roadmap for the Implementation of Sex and Gender in European Biomedical and Health Research

The kick-off conference laid the foundation for the next stage of EUGenMed that will elaborate the detailed content of the Roadmap during five workshops taking place between November 2014 and April 2015 in Berlin, Maastricht and Brussels. Experts and a diverse group of stakeholders such as researchers, policy makers, patient organisations, non-governmental organisations (NGOs), funding and regulatory bodies, health insurance providers, pharmaceutical companies, medical societies, health education organisations, and the media will assemble state-of-the-art knowledge about sex and gender. The workshops will include in (1) clinical research and clinical pharmacology, (2) public health and prevention, (3) basic research and pre-clinical drug development, (4) medicines regulation, and (5) medical education. The invitations for the first and second workshops, which will respectively cover (1) sex and gender differences in coronary heart disease, heart failure and arrhythmia and (2) sex, gender and risk factors for non-communicable diseases across Europe are already being sent.

The outcomes of these workshops will be position papers with specific recommendations and materials to allow for communication and dissemination to a wider audience. The information gathered will contribute to the EUGenMed roadmap for the implementation of sex and gender in European biomedical and health research and will be presented at the closing conference at the end of 2015. Exciting challenges lie ahead, but with the committed involvement of experts and stakeholders, we are confident that we will be able to draw up a Roadmap that provides clear recommendations and guidance for sex and gender to be implemented in European biomedical and health research.



Figure 7. Participants in the EUGenMed Kick-off Conference in Brussels on April 7th, 2014

We now are inviting all interested experts, stakeholders and citizens to get in touch with the EUGenMed consortium and to participate in building a strong European Gender Medicine network for the implementation of sex and gender in biomedical and health research in Europe to improve the health of all EU citizens, both men and women.



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