Gender equality and gender dimension in academic research - how to define excellence

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“the gender dimension is explicitly integrated into several topics across all the sections of the Work Programme” (…)

“a topic is considered gender relevant when it and/or its findings affect individuals of groups of persons. In these cases, gender issues should be integrated at various stages of the action and when relevant, specific studies can be included”.

Integrating a gender dimension means paying attention to sex differences and gender effects in the content of research; different relevance for different fields of sciences;
Topics today

- Are Sex and Gender (S&G) important topics in academic medicine?
- Gender in medical education
- How to organize gender medicine
- Are gender equality and gender dimension in research related?
- What is excellent (gender) research?
Sex and Gender (S&G) are related in medicine

**Sex – biological facts, Genes and Hormones**

- **X**: ca 1500 Genes
  Heart-, Brain-, Immune function

- **Y**: 78 Genes
  Sexual function

**Gender – Socio-cultural facts**

- Biological sex affects behaviour

- Environment leads to epigenetic chromatin modifications
S&G differences in cardiovascular disease - Higher early mortality in women with MI

Mortality after MI  2005 in Berlin, 5000 patients

Retrospective US study on 384,878 pat. - 40% women

Higher early mortality in women with MI
Problem: Women with MI arrive later in hospital than men

<table>
<thead>
<tr>
<th>Country</th>
<th>Condition</th>
<th>Intervall : Onset of symptoms - medical contact</th>
<th>Intervall: medical contact – hospital admission</th>
<th>Hospital admission - intervention</th>
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<td>France, all</td>
<td>STEMI</td>
<td>M 200 / W 245</td>
<td>Donataccio, 2015</td>
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<td>NL</td>
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<td>&lt;65 y: 150 / W 165</td>
<td>Men=women</td>
<td>Otten, 2013</td>
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<td>154 / W 189</td>
<td>Ladwig, 2009</td>
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<td>SW</td>
<td>STEMI</td>
<td>169 / W 190</td>
<td>Von 51/ 80 auf 43 / 48 nach intervention</td>
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<td>STEMI</td>
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Acute coronary syndromes: S&G differences in presentation

Heart disease is the No. 1 killer of women, yet American research shows that only one in four women realize it is a greater threat than cancer • A woman has a 50% chance of dying from her first heart event, compared with a 30% chance for a man • Of those who survive their first heart attack, 38% of women will die within a year, vs. 25% of men • 46% of women are disabled by heart failure after a heart attack, compared with 22% of men
Why is there no research on mechanisms for S&G differences?

Figure 1 Anatomical and functional components of cardiac pain generation.
Problem: High rate of normal angiographies in women with chest pain

Figure 1: Proportion of patients undergoing first-time diagnostic coronary angiography according to age (years) and sex.

Figure 3: Proportion of patients with normal findings at coronary angiography according to age group and sex.

Johnston et al, EHJ 2011
Specific features of middle aged women

- Premenopause
  - Low risk

- 45-65 years
  - Low-intermediate risk
  - Less obstructive CAD than in men
  - Coronary microvascular disease
  - Coronary dissections

- Older age
  - High risk

EUGENMED study group, EHJ, 2015
Differences in vascular pathophysiology in women and men

More frequent in men:
localized stenoses

More frequent in women:
non-obstructive CAD (NobCAD)
Wall thickening,
microembolism, spasms,
endo-thelial dysfunction

Mering G, Circ 2004; Bugiardini R, Merz NB JAMA 2005

www.charite.de/gender
Spasms in the big vessels are frequent in women.
Emotional Stress – physical activity as inducers of MI in women and men

Metaanalyse (17 Studien) Čulić et al., Int J Cardiol (2005)
Stress induced cardiomyopathy: Tako tsubo, occurs in > 90% in women

Mimics myocardial infarction
But normal coronary arteries
Severe disease
Triggered by massive psychological stress

Was believed to be extremely rare –
German registry with more than 300 pts in 2 years

Now starting: Berlin Heart and Soul study – BEHERS – to identify
• Mechanisms and
• Novel treatment approaches in Tako tsubo

Sharkey, Circulation 2005
Tako-Tsubo – 70 – 90 % women

8 % of acute coronary syndromes in women

Mechanisms:
Sex specific activation of ß AR
Decrease in estrogens
Defect in microcirculation?

BEHRS study at Charité/GIM
Rare complication: Cardiac rupture

Extreme manifestation of women – typic heart disease
- Highly understudied, mortality 8 %
- Animal model: male rat
Basic research – mainly male animals

Proportion of Research Studies Using Male and/or Female Animals
From published journal articles within specified biomedical subfield, 2009

Drug development should be done in male and female mice - example: survival after MI!

Improvement is seen in the whole cohort and in males, not in females.

**Males!**

Improvement in survival after MI with therapy in males.

**Females**

Improvement in survival after MI with therapy in females.

**All!**

Improvement in survival after MI with therapy in the whole cohort.
Human ventricular myocytes

Cristina E. Molina, Barcelona, Spain
Sex differences in mechanistic pathways of heart failure - dilated cardiomyopathy

- Gene expression in LV samples of end-stage non-ischaemic DCM patients

![Venn diagram showing gene expression differences between males and females with DCM.]

False discovery rate (FDR)-adjusted $P < 0.01$

Kararigas et al., unpublished
Sex differences in molecular pathways for heart failure - drug targets

Yellow indicates **induction** and purple **repression**

**male**: Proteasome, Oxidative phosphorylation, Calcium signalling pathway, Natural killer cell mediated cytotoxicity, Cytokine-cytokine receptor interaction

**female**: Wnt signalling pathway, mTOR signalling pathway, Hedgehog signalling pathway, Tight junction, Calcium signalling pathway

Kyoto Encyclopedia of Genes and Genomes; 1000 permutations; adjusted $P < 0.05$
Consequences on unbalanced research:

Data from 48 cohort studies for novel drugs

![Graph showing age and sex distribution of suspected ADRs]

- **285,862 Frauen**
- **221,781 Männer**

Figure 1: Age and sex specific incidence rates of suspected adverse drug reactions (ADRs) ■ female, ▲ male.

Martin RM, Br J Clin Pharmacol; 46: 505-511
Sex differences in the effects of digitalis

1997: Digitalis-Study – Improvement of morbidity in HF by digitalis, no effect on mortality: inclusion in guidelines

2002: First sex-specific analysis

Over-mortality in women with digitalis!

Rathore et al, NEJM 347:1403, 2002
Heart transplantation – Deutsches Herzzentrum Berlin

n = 1263

- m → m: 768 (61%)
- m → f: 83 (6.5%)
- f → f: 146 (11.5%)
- f → m: 266 (21%)

Males receive 82% of organs

Same in kidney transplant
Who does gender research?

- Gender congress, September 2015 in Berlin, BMBF
- Congress of International Society of Gender Medicine
- 300 participants
Mainly women
Where does the money go?

Founding Members of German Centre for Cardiovascular Research (DZHK)

- DZHK unifies the 7 most excellent Cardiovascular Research Centres in Germany – 42 Mill funding/year
What is excellent?

- Detecting novel molecular mechanisms?
- Describing sex differences in animal models or human heart?

Who defines excellence?
Comment organiser les études en médecine de genre?

Sexe et genre s’appliquent sur toutes les disciplines médicales de manière transversale

Les études sexe/genre simples et sans hypothèses – nombres hommes femmes,..... - n’aident souvent pas pour faire avancer les sciences

Excellence: Hypotheses
Études des mécanismes
Voies de formation
Perspectives professionnelles pour les jeunes

La médecine de genre doit être une discipline propre!

Académie Française, Dec 2015
How to implement gender research - models

- **NIH**: will require all grant applicants “to report their plans for the balance of male and female cells and animals in preclinical studies in all future applications, unless sex-specific inclusion is unwarranted, based on rigorously defined exceptions [1].”

- **CIHR** “expects that all research applicants will integrate sex and gender into their research designs when appropriate…. There is no simple "recipe" for integrating sex and gender in health research .....”

- Horizon2020: mentions in some calls, that S&G should be analysed

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**However:**

Not all applicants may have S&G expertise

Training centers needed

Truely focused studies on mechanisms of S&G are not included here
Example for mechanistic studies: developing a concept for gender

Gender distribution in men and women with premature acute coronary syndrome.

Sex als and Gender are associated with cardiovascular risik faktors

L Pilote, Psychosomatic medicine 2015
Modular Medical Curriculum at Charité: Integration of gender and sex aspects

### Practical Year (Internal Medicine, Surgery, Elective)

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<tr>
<th>Module</th>
<th>Title</th>
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<td>S10</td>
<td>General Medicine, „Paper Work“</td>
<td>Emergency Medicine, Interfaces M38</td>
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<td>Practical Courses: Internal Medicine, Surgery, Pediatrics</td>
<td>Gynecology M39</td>
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<td>Revision Course II M40</td>
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<td>Old Age, Death and Dying, Intensive Care, Palliative Medicine M36</td>
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<td>Neoplasia as Disease Model M19</td>
<td>The Mind and Pain as Disease Model M20</td>
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<td>Human Beings and Society M6</td>
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<td>Signal and Information Systems M4</td>
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Welcome to this interactive, web based eLearning platform eGENDER!

eGENDER Medicine

Use the eLearning course eGENDER Medicine for your personal education in Gender Medicine. You are independent of place and time. The Institute of Gender in Medicine (GIM) - Charité University Medicine Berlin developed this advanced training course based on systematic analysis of gender differences in basic and clinical research. Doctors should be able to integrate these concepts into clinical medicine and use the sex perspective for assessment in their daily practice.

Awareness of gender differences is nowadays accepted as a quality parameter in medicine. The term "gender" integrates behavioural, life style, environmental and stress factors as well as genetic variables and is not easy to replace by other parameters.

The author reviewed and worked up most interesting material of major medical disciplines based on the European curriculum of "Gender Medicine" provided by internationally renowned experts of Gender Medicine.

Social contacts to other students and experts are intended to being intensified with the possibility to use "communicative tools" like forum, chat and wiki. This is exactly what we desire to support an active "gender medicine community"! "Gender Medicine" is a new and challenging research field of medicine that aims to assure an improved health care for both women and men around the world.
Horizon 2020 Gender Equality provisions

How to organize research?

Gender balance in decision making!

Gender balance in research teams at all levels

Gender dimension in R&I content, and in teaching
Danksagung

Barcelona
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