Sex and Gender in Medicine

Gendermedizin
Der lange Weg zur Chancengleichheit

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Gender Medicine

Study of how diseases differ between men and women in terms of prevention, manifestation, therapeutic responses, prognosis, and social impact.

Gender-specific Medicine is a neglected dimension of medicine
Sex AND Gender Impact Health and Disease

Sex and Gender in Medicine

Interrelation of Sex and Gender

Sex

Biological differences such as genes, sex hormones, anatomy, and physiology

Gender

Socially constructed characteristics of women and men

Mauvais-Jarvis F et al. Lancet. 2020
Interrelation of Sex and Gender

Potential Epigenetic Mechanisms Influencing Sex Differences in Acute Coronary Syndrome (ACS) Pathogenesis

- Risk Factors
  - Lifestyle
  - Obesity
  - Dyslipidemia
  - Hypertension
  - Diabetes
  - Plaque rupture

DNA Strand
RNA Strand
miRNA
IncRNA
DNA Methylation
Histone Modification
Histone
ACS

Haider A [...] Gebhard C. Eur Heart J. 2019
Sex Chromosomes

- In men, the X chromosome carries only maternal imprints.
- Women have X chromosomes from both parents.
- Random inactivation of one of the X chromosomes occurs in female cells.
- Some of these X-linked genes escape inactivation in women, those genes are often expressed at higher levels in women than in men.
Sex Chromosomes: Cancer Risk

• The majority of non-reproductive cancers exhibit a 2:1 or even higher male predominance

• Male predisposition to glioblastoma: incomplete X-inactivation in female individuals which results in bi-allelic expression of X-encoded tumour suppressors in female cells

• Y chromosome-encoded oncogenes in male cells
Sex Chromosomes: Immune Responses

Pneumonia

- The increased susceptibility of men to pneumonia is hypothesised to result from X-linked genes.
- The fact that women carry two X chromosomes could provide them with a greater genetic diversity to combat infection than men.

Myocarditis

- Men are more likely to develop myocarditis and post-myocarditis heart failure than women.

Sex Differences in Immune Responses

Vaccination: X-linked genes in B-lymphocytes

- Women develop a higher quality and quantity of antibodies than men following vaccination
- Antibody response of females to a half dose of influenza vaccine was equivalent to that of a full dose in males
- Vaccine hesitancy is higher among women
- Women more frequently report adverse events following immunization

Implications for Vaccination Trials

Lack of high-quality research investigating sex differences in vaccine immunogenicity, effectiveness, or safety.

Currently more than 200 vaccine candidates against SARS-CoV-2 underway, of which over 45 have advanced to clinical trials -> unique opportunity to investigate sex-specific immune responses

To be assessed: different doses, different intervals, different vaccine candidates (viral vector, nucleosid vaccines, inactivated viruses, proteins), impact of hormonal cycling on vaccine response

Fathi A et al. Front Immunol. 2021
• **Immune checkpoint inhibitors** can improve survival for men with advanced **melanomas** and **non-small cell lung cancers** more than for women.

• The molecular subtyping of **glioblastomas** based on sex-specific transcriptomes has the potential to enhance chemotherapy in a sex-specific manner.

• Sex differences in xenobiotic metabolism regulatory networks might underlie greater treatment response of women with **colon cancer** and require modification of approaches for men.
Gender – Risk Behaviour

• Men are more likely to eat unhealthy diets, exercise less, consume alcohol, smoke, misuse drugs, or exhibit risky behaviour.

• Men are socially conditioned to neglect pain and disease, resulting in a general underutilisation of health services and a lower likelihood to engage in routine checks.

• Life expectancy: Despite women being often misdiagnosed, premature mortality in men is twice as high as in women in Europe.
Gender – Liver Disease

• **Alcoholic liver disease** is more common among men because men have a higher alcohol consumption than women.

• Threshold amount of alcohol that results in alcoholic liver disease in women is half that of men.

• Due to sex differences in ethanol metabolism, women have higher blood ethanol concentrations than men after drinking the same amount of alcohol.
Sex and Gender Impact Disease Manifestation and Outcomes: COVID-19

Where are the women? Gender inequalities in COVID-19 research authorship

Ana-Catarina Pinho-Gomes, Sanne Peters, Kelly Thompson, Carinna Hockham, Katherine Ripullone, Mark Woodward, Cheryl Carcel

Sex and Gender Impact Disease Outcomes: COVID-19

PROTECTS FROM POST-COVID-19
- Pregnancy
- Child care

POST-COVID-19 IN WOMEN AND MEN

- Depression: 43%
- Stress at home: 33%

INCREASES RISK OF POST-COVID-19
- Cardiovascular disease
- Obesity
- Being responsible for housework
- Child care
- Pregnancy
- Cardiovascular risk factors
- Femininity
- > 5 symptoms ICU stay

N=2799 patients in Switzerland
Sex and Gender May Exert Opposite Effects

Sex and Gender in Medicine


Larger myocardial infarct size in male mice, which is attenuated following orchiectomy

Infarct volume (mm$^3$) Female Male

In red: Female, in blue: Male

Women

Men

21.1% [18.7%-23.8%]

16.2% [15.0%-17.6%]

p=0.010

p=0.054

Days after myocardial infarction

Event rate (%)

p=0.0002

MRI

Larger myocardial infarct size in male mice, which is attenuated following orchiectomy

Haider A [.....] Gebhard C. Manuscript submitted
Gender Differences in the Provision of Care: the ‘Yentl’ Syndrome


N=450’948 patients in Switzerland:
Women with cardiovascular disease less likely to receive intensive care
Although women more often donate kidneys and show similar transplantation survival benefits than men, women still receive fewer kidney transplants.
The ‘Yentl’ Syndrome: Endocrinology

**Dyslipidaemia:** less often treated in women.

**Diabetes:** stronger risk factor for the onset of ischaemic heart disease, heart failure, stroke, cancer, and dementia in women than in men, but undertreated in women. Diabetes-related mortality has dramatically decreased in men, but less so in women.

**The ‘Yentl’ Syndrome: Prevention**

**Primary prevention:** The incidence of lung cancer is increasing in women, but non-smoking campaigns are more fruitful in men.

**Secondary prevention:** Women are less likely to be referred for rehabilitation.
Sex and Gender Differences in Treatment Responses

Women experience more often treatment complications

n=2'200

Women
Men

Complications (%)

p<0.05
p<0.05
p=NS

Succesful Intervention (%)

p=NS
p<0.05

Women
Men

Women
Men

Experience more often treatment complications

Gebhard C et al. Clin Res Cardiol. 2018
Sex and Gender Differences in Treatment Delays

Women with an acute myocardial infarction experience significant treatment delays

Average treatment delays
Men: 1.4 – 3.5 hours
Women: 1.8 – 7.2 hours

“Prehospital delay in persons with symptoms of acute myocardial infarction has remained essentially unchanged during the 20-year period”

Sex and Gender Differences in Pain Perception


- Dyspnea
- Chest pain
- Palpitations
- Back pain
- Abdominal pain
- Vomiting
- Nausea
- >3 symptoms

% of patients

Men vs. Women

Infarction pain
Sex and Gender Differences in Pain Perception

Women are more sensitive to pain...

Heat stimulus

Men more sensitive

Women = Men

Women more sensitive

P < 0.0001

Number of studies

10

20

30

40

50

Cold stimulus
Sex and Gender Differences in Pain Perception

…and suffer more often from chronic pain
Sex and Gender Differences in Pain Perception

Dopamin, a neurotransmitter mediating pain perception, is being ingested twice as fast in female neurons as compared to male neurons.

Estrogen modulates activity of sensory neurons.

The Bias

...but:

79% of animal studies in pain perception have been conducted in male animals
The Bias: Lack of Sex-specific Data in Basic Science

Animal studies

Cells

Genetics

- Male only
- Female only
- Both sexes — no differences
- Both sexes — differences
- Sex not reported

Male 20%
Female 5%
Not defined 75%
The Bias: Clinical Trials

Only 18-24% of study participants in cardiovascular clinical trials are female.

The percentage of female cardiovascular patients amounts to 53%.

Bikini-Medicine
Women’s health research focuses on breasts and the reproductive system

The Bias: Recent Example

Sex and Gender in Medicine

The NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Colchicine in Patients with Chronic Coronary Disease


• Sex differences in inflammation/immune responses are known
• 15% women, 85% men
• No benefit in women (supplementary information)
Sex and Gender in Medicine

The Impact: More Side Effects in Women

Meta-analysis comprising 48 studies, Br J Clin Pharmacol. 1998
The Impact: Overdosing in Women

**Men:** lowest risk at 100% of recommended dose

**Women:** lowest risk at 40-60% of recommended dose

Santema BT et al. Lancet. 2019
The Impact: Overdosing in Women

Dialysis overdose or administration of larger-than-needed amounts of EPO-stimulating agents among women are attributed to extrapolating men’s therapeutic dosing to women.

Women on dialysis have higher hospitalisation rates, lower reported quality of life, and greater symptom severity than men.

Growing Public Interest

Female mice liberated for inclusion in neuroscience and biomedical research

Sex and Gender in Medicine

Offline: Gender and global health—an inexcusable global failure

Sex Differences in Outcome Measures After Stroke

Osteoporosis Significantly Underdiagnosed, Undertreated in Men

Are Women Less Likely to Receive High-Intensity Statins After MI?

More Women Dying Of Heart Disease, Yet Men Still Get More Treatment

Pharmacologic Research in Pregnant Women — Time to Get It Right

Myocardial Infarction in Young Women: An Unrecognized and Unexplained Epidemic

Inequality in medicine

Regulators have been calling for equal representation of men and women in nearly 25 years. So why are women still underrepresented?

Adverse Drug Reactions to Guideline-Recommended

Covid Kills More Men Than Women. Experts Still Can't Explain Why

A new tracker from Harvard’s GenderSci Lab is the first to consolidate sex-separated data from across the US. It may help researchers solve the mystery.

Outcomes in liver transplantation: Does sex matter?

Women Twice as Likely to Develop Depression After Stroke

Minor Stroke, TIA Diagnosis More Often Missed in Women

cdoi.org/10.1093/lmv/hwaa146

Clinical trial enrolment favours men

Women's Alzheimer's going undiagnosed because of better memory for words, study indicates

BETTER MEDICINE

Gender Gap Still Wide Open as US Data Show Men Have Consistently Better PCI Outcomes

FDA Takes Action on Ambien; Concedes Women at Greater Risk

THE YENTIL SYNDROME

Bernadine Healy, M.D.

Sex Differences in Efficacy and Toxicity of Systemic Treatments: An Undervalued Issue in the Era of Precision Oncology

Sex Differences in Cardiovascular Disease and Cognitive Impairment: Another Health Disparity for Women?

FDA analysis: Women underrepresented in HF, CAD, ACS trials

The Feminine Face of Ischemic Heart Disease

Challenges and Opportunities°
Recent Parliamentary Interpellations 2019/2020

20.3092 MOTION

Geschlechterunterschiede als Thema in der medizinischen Lehre und Forschung

Eingereicht von: PORCHET LÉONORE
Grüne Fraktion
Grüne Partei der Schweiz

Einreichungsdatum: 11.03.2020
Eingereicht im: Nationalrat
Stand der Beratungen: Im Rat noch nicht behandelt

20.3093 POSTULAT

Gesundheitswesen durch die Gleichstellungsbrille betrachten

Eingereicht von: PORCHET LÉONORE
Grüne Fraktion
Grüne Partei der Schweiz

Einreichungsdatum: 11.03.2020
Eingereicht im: Nationalrat
Stand der Beratungen: Im Rat noch nicht behandelt

19.3910 POSTULAT

Gesundheit der Frauen. Bessere Berücksichtigung ihrer Eigenheiten

Eingereicht von: FEHLMANN RIELLE LAURENCE
Sozialdemokratische Fraktion
Sozialdemokratische Partei der Schweiz

Bekämpfer/In: SCHLÄPFER THERES

Einreichungsdatum: 21.06.2019
Eingereicht im: Nationalrat
Stand der Beratungen: Angenommen

19.3577 MOTION

Homo mensura. Der Mann, das Mass in Forschung und Medizin?

Eingereicht von: HEIM BEA
Sozialdemokratische Fraktion
Sozialdemokratische Partei der Schweiz

Übernommen von: MUNZ MARTINA

Einreichungsdatum: 11.06.2019
Eingereicht im: Nationalrat
Stand der Beratungen: Im Rat noch nicht behandelt

Source: Catherine Fussinger, Gender Health Network Meeting 2020, presentation slides
• **National Institutes of Health**: issued its mandate for including females in vertebrate studies

• **Canadian Institutes of Health Research**: expects that all research applicants will integrate sex and gender into their research design when appropriate

• Gender policy committee of the **European Association of Science Editors** recommends that journal editors should ask all authors to report their results separated by sex and gender.

• **The International Committee of Medical Journal Editors** (ICMJE) integrated sex and gender analysis into its guidelines in December 2016

• The **Lancet** and Sex and Gender Equity in Research (SAGER) have published guidelines for authors and journal editors for evaluating manuscripts for excellence in sex and gender analysis.

• **UK National Centre** for the Replacement, Refinement and Reduction of Animals in Research has issued guidelines calling for basic research to **always** report the sex of lab animals.

• **Horizon 2020**: sex and gender must be integrated into all stages of research and innovation
Summary

- Disease occurrence, clinical manifestations, and outcomes differ between men and women.
- Sex- and gender-specific approaches hold promise to improved cancer prevention and treatment.
- Women and men are most of the time treated similarly, which is often based on experimental and clinical data over-representing one sex.
- Sex-unspecific therapeutic strategies always adversely affect one sex by causing differences in therapeutic success and adverse reactions.
- There is lack of awareness amongst health care professionals and researchers that sex- and gender-differences exist.
- This contrast with increasing public awareness of sex- and gender differences in medicine.
- Studying both sexes will become a requirement in the upcoming years.
Current Efforts to Close Knowledge Gaps

- Continuing Education course of the Universities of Bern and Zurich Zürich
- Next start spring 2022
- 11 modules
- Across all disciplines
- For health care professionals, researchers and industry
- https://www.gender-medicine.ch/

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<td>Introduction to Gendermedicine</td>
<td>University of Bern Mittelstrasse 43</td>
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<td>12 – 13 April 2021</td>
<td>Cardiovascular medicine</td>
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<td>Infectious Diseases</td>
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Thank you!

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