BURDEN OF CHRONIC DISEASE:
WHY IS THERE A SEX & GENDER GAP?

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Disclosure

No relationship or financial conflicts of interests to disclose.

The statements and opinions expressed are those of the speaker and do not represent NIH or the University of South Carolina policies or official stance.
Overview

Terminology
National Impact of Chronic Illness
Limitations in Current Health Policies
Bias and Biology
Call to Action
Terminology Matters

Those who forget history are destined to repeat it
Chronic illnesses are “conditions that last a year or more and require ongoing medical attention and/or limit activities of daily living.”

Duration: ≥1 year

Functional limitation: yes

Need for ongoing medical care: yes

This definition, adapted from other sources, incorporates elements of duration, medical requirements, and functional status. It also has the advantage of being compact. The HHS Strategic Framework also adopts the definition of “multiple” used in another source as 2 or more concurrent chronic conditions.
An NIH-wide definition of chronic debilitating conditions in women does not currently exist.
Sex is the classification of living things, generally as male or female according to their reproductive organs and functions assigned by the chromosomal complement.

Gender is defined as a person’s self-representation, or how that person is responded to by social institutions on the basis of the individual’s gender presentation.

Source: Exploring the Biological Contributions to Human Health: Does Sex Matter (2001)
Frequency of the term Gender Interchanged with Sex

Number of article titles from 1960 to 2004 examined by the authors in which the term gender was used as an equivalent term for sex in sex-based research publications in the Journal of Applied Physiology and journals of the American Physiological Society.
Impact of Chronic Illness
CDC's National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP)

CHRONIC DISEASES IN AMERICA

6 IN 10 Adults in the US have a chronic disease

4 IN 10 Adults in the US have two or more

THE LEADING CAUSES OF DEATH AND DISABILITY and Leading Drivers of the Nation's $3.8 Trillion in Annual Health Care Costs

THE KEY LIFESTYLE RISKS FOR CHRONIC DISEASE

HEART DISEASE, CANCER, CHRONIC LUNG DISEASE, STROKE, ALZHEIMER'S DISEASE, DIABETES, CHRONIC KIDNEY DISEASE
## Leading Causes of Death, by Sex

### All races and origins\(^1\), Male, All ages\(^2\)

<table>
<thead>
<tr>
<th>All races and origins, Male, All ages</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Heart disease</td>
<td>24.2%</td>
</tr>
<tr>
<td>2) Cancer</td>
<td>21.9%</td>
</tr>
<tr>
<td>3) Unintentional injuries</td>
<td>7.6%</td>
</tr>
<tr>
<td>4) Chronic lower respiratory diseases</td>
<td>5.2%</td>
</tr>
<tr>
<td>5) Stroke</td>
<td>4.3%</td>
</tr>
<tr>
<td>6) Diabetes</td>
<td>3.2%</td>
</tr>
<tr>
<td>7) Alzheimer’s disease</td>
<td>2.6%</td>
</tr>
<tr>
<td>8) Suicide</td>
<td>2.6%</td>
</tr>
<tr>
<td>9) Influenza and pneumonia</td>
<td>1.8%</td>
</tr>
<tr>
<td>10) Chronic liver disease</td>
<td>1.8%</td>
</tr>
</tbody>
</table>

### All races and origins\(^1\), Female, All ages\(^2\)

<table>
<thead>
<tr>
<th>All races and origins, Female, All ages</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Heart disease</td>
<td>21.8%</td>
</tr>
<tr>
<td>2) Cancer</td>
<td>20.7%</td>
</tr>
<tr>
<td>3) Chronic lower respiratory diseases</td>
<td>6.2%</td>
</tr>
<tr>
<td>4) Stroke</td>
<td>6.2%</td>
</tr>
<tr>
<td>5) Alzheimer’s disease</td>
<td>6.1%</td>
</tr>
<tr>
<td>6) Unintentional injuries</td>
<td>4.4%</td>
</tr>
<tr>
<td>7) Diabetes</td>
<td>2.7%</td>
</tr>
<tr>
<td>8) Influenza and pneumonia</td>
<td>2.1%</td>
</tr>
<tr>
<td>9) Kidney disease</td>
<td>1.8%</td>
</tr>
<tr>
<td>10) Septicemia</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

[1](https://www.cdc.gov/women/lcod/index.htm)
Evidence is provided through well-designed, well-conducted, and optimal reporting of research.

Healthcare is evidence-based.

Without the data, cannot find the answer.
Biological Plausibility
### Sex bias in infectious diseases, inflammatory diseases, and cancers

<table>
<thead>
<tr>
<th>Autoimmune diseases</th>
<th>Infectious diseases</th>
<th>Non-reproductive cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Graves disease</td>
<td>• HIV</td>
<td>• Bladder</td>
</tr>
<tr>
<td>• Hashimoto thyroiditis</td>
<td>• Influenza</td>
<td>• Bowel</td>
</tr>
<tr>
<td>• Multiple sclerosis</td>
<td>• Toxoplasmosis</td>
<td>• Kidney</td>
</tr>
<tr>
<td>• Rheumatoid arthritis</td>
<td>• Legionella</td>
<td>• Leukaemia</td>
</tr>
<tr>
<td>• Systemic lupus erythematosis</td>
<td>• Malaria</td>
<td>• Liver</td>
</tr>
<tr>
<td>• Type 1 diabetes</td>
<td>• Zika</td>
<td>• Lung</td>
</tr>
</tbody>
</table>

Research Environments and Research Expenditures Directly Impact the Burden of Chronic Diseases

Knowledge Transfer and Application Occurs Across Environments

- Discovery
  - NIH
- Product Development
- Approval/Post market
- Industry
  - FDA

Presented as FDA Commissioner’s Proxy to the Congressional Task Force on Research Specific to Pregnant Women and Lactating Women (2018) Source: M. Jenkins
THE BIASED RESEARCH PIPELINE

Source: Jenkins M. TTUHSC Laura W. Bush Institute for Women’s Health
Health Policies Which Enable Understudy and Underreporting of Sex and Gender Differences
NIH Inclusion NIH Revitalization Act

FDA Guidance: both sexes of animals in preclinical studies

FDA Gender Guidance in Drug Evaluation

FDA Office of Women’s Health created

FDA Clinical Hold Rule instituted

FDA GAO Study: 8/10 drugs withdrawn had more adverse events in women

FDA Drug Trial Snapshots, Women’s Health Research Roadmap

NIH policy: both sexes of cells

Public Health Task Force Report: Women’s Health

NIH GAO Report: Women underrepresented, data not analyzed

NIH Inclusion Policy

NIH GAO Report: Inclusion Policy No data tracking

NIH Revitalization Act NIH ORWH created

NIH GAO Study: Lack of data tracking

IOM Report: Does Sex Matter?

NIH policy: both sexes of cells and vertebrate animals

GAO Study: Women 57% of CT subjects No data tracking

FDASIA 907 Congressional Mandate & Action Plan


1977 FDA Policy: No women of childbearing age in early phase clinical trials

1985 NIH Inclusion Policy
FDA Policy: No Women of Childbearing Age in Early Phase Clinical Trials

- FDA recommended that **premenopausal women capable of becoming pregnant** be **excluded** from early phases of drug trials.
- “Capable of becoming pregnant” included women using reliable methods of contraception, women whose male partners had had vasectomies or used condoms, and women who were "single."
- Pertained only to early phases of drug development, but in practice the **participation of women in all phases were affected.**
NIH Inclusion Policy

• **Consider the inclusion** of women in the study populations for all clinical research efforts.
• General differences **should be** noted and evaluated.
• If women are not to be included, a **clear rationale** should be provided for their exclusion.
1993
FDA Guidance: Gender Differences in Drug Evaluation

1990
GAO Study: NIH
GAO Study: NIH

- NIH policy on inclusion of women in clinical trials was not well communicated or understood within NIH or research community.
- Was applied inconsistently among institutes, and was applied only to extramural research.
- There was “no readily accessible source of data on the demographics of NIH study populations,” so it was impossible to determine whether NIH was enforcing its own recommendations.
FDA Guidance: Gender Differences in Drug Evaluation

- Encourages inclusion of women in phase I and II studies
- Expects inclusion of women in efficacy studies
- Expects analysis of data in regard to race, age, gender**
1993
NIH
Revitalization Act
Office of Research on Women’s Health Created

1998
FDA Demographic Rule
NIH: Revitalization Act ORWH Created

- Women & minorities to be included in clinical research

- Ensure that valid scientific analysis *could be* performed in determining whether differences existed between women and minorities in relation to other study subjects

- Include both sexes in adequate numbers to ensure data *could be* analyzed for an effect of gender on safety and efficacy of proposed intervention or drug.
1998

**FDA Demographic Rule**

**REQUIRES** sponsors to:

- **Tabulate** the trial population by age group, sex, and race in Investigational New Drug (IND) applications

- **Analyze safety and efficacy** by age group, sex, race, and other variables as appropriate in New Drug Applications (NDA)
2000
Final Rule: FDA (Clinical Hold): NIH

2000
GAO Study: NIH
GAO Study: NIH

- Women are in clinical trials at rates proportional to their numbers in general population, however...
- NIH lacked protocols to enforce the mandate to perform and report valid scientific analysis of sex differences in late stage (Phase III) clinical trials
- NIH lacked adequate data tracking of women and minorities enrolled in trials
- This lack of compliance could significantly impact the ability to apply sex differences research to clinical management and outcomes
FDA Final Rule Clinical Hold

Permits the Agency to place a clinical hold on an investigational new drug application if men or women with reproductive potential are excluded from participation only because of the risk or potential risk of reproductive or developmental toxicity associated with use of the investigational drug.
2016 NIH Sex as a Biological Variable Policy

2015 NIH GAO Audit
2015 NIH GAO Study

57% of 2014 NIH-funded CT subjects were women

Does not track whether study includes plans for analysis by sex

Lacks summary data to identify potential sex differences

Limits assurance that NIH is supporting research that can inform medical practice for both women and men
2016 NIH SABV Policy

- **Consideration of sex may be** critical to the interpretation, validation, and generalizability of research findings.

- Appropriate analysis and transparent reporting of data by sex **may therefore** enhance the rigor and applicability of preclinical biomedical research.

- NIH **expects that sex as a biological variable** will be factored into research designs, analyses, and reporting in vertebrate animal and human studies.

- Strong justification from the scientific literature, preliminary data, or other relevant considerations **must be provided** for applications proposing to study only one sex.

- Investigators **are strongly encouraged** to discuss these issues with NIH program staff prior to submission of applications.
“The NIH is engaged in ongoing efforts to develop resources to help investigators consider SABV in their research.”
21st Century Research Crisis: Pregnant Women and Lactating Women
21\textsuperscript{st} Century Cures Act (Sec 2041) 
Research Specific to Pregnant Women and Lactating Women
(\textit{PRGLAC}) Task Force
\textit{Phase 1 2017-2018}

PRGLAC Task Force Recommendations
PRGLAC Report: page 34 and Appendix page 368 describes finding of an audit of
drug labeling regarding safety and efficacy in pregnant and lactating women

\textbf{The lack of human data is striking.}
\url{https://www.nichd.nih.gov/about/advisory/PRGLAC/recommendations}. 
FDA staff identified a total of 575 prescription drug and biological product labeling changes (including labeling for new products) approved in PLLR format between June 30, 2015-September 30, 2017.

- 129 (22.4%) included human data about pregnancy
- 86 (15.0%) included human data about lactation
- 50 products (8.7%) included human data about both pregnancy and lactation
- 414 products (72%) had neither human data about pregnancy nor human data about lactation.

We continue to protect women from research instead of with research (quoted by many)
NIH ORWH Cannot Advance The Health Of Women Alone

Achieving true progress requires change across many organizations and institutions
Points of Engagement:
Integrating Sex and Gender into Research, Education, and Clinical Care

Examples: Not All-Inclusive

**Accrediting & Certification:**
LCME, ACGME, NBME

**Curriculum Gatekeepers**
Deans of Curriculum, Block Leaders, Educational Policy Committee

**Curriculum Integration Committee**
Core Faculty Group Leading the Curriculum Integration

**Emerging Technologies**
Smart Phone and Tablet Apps

**Faculty Champions**
Grass-roots engagement of Basic and Clinical Faculty to Pioneer Efforts and Engage Others

**Institutional Leadership**
President, Deans, Assoc/Asst Deans, Chairs

**Leading Sex & Gender Academic Health Centers**
Mayo Clinic, UCSF, UCLA, TTUHSC, Univ of Wisc, Yale

**Gender Medicine-Focused Organizations & Initiatives**
SWHR, SGWHC, IGN, NAMS, OSSD, LWBIWH

**Government Organizations**
DHHS OWH, FDA, NIH ORWH, HRSA, CDC, NSF

**Medical Database/Search Engine**
PubMed, Ovid, Up-to-Date, Medscape, MD Consult

**Journals & Other Scientific Publications:**
Peer Reviewers, Editors, and Publishers

**Media**
Monographs, Reviews, Commentaries

**Specialty Organizations**
AAFM, ABIM, ACP, ACOG, APGO, AMSA (many more)

**Social Media**
Blogs, Twitter, Facebook, LinkedIn

**Webinars & Online CME**
Medscape, Web MD, NIH ORWH, LWBIWH CME

Source: M. Jenkins
MORE WOMEN PARTICIPATING IN RESEARCH BUT WITHOUT MARKED PROGRESS IN OUTCOMES AND CLINICALLY MEANINGFUL KNOWLEDGE OF SEX AND GENDER DIFFERENCES

FDA and NIH health policies include language such as might, may, could, should which (as we have and will hear from the presentations today) result in research design and reporting by sex and gender optional....and as the data shows...far too many researchers have opted out.

This causes inequity in the application of scientific discovery across research and clinical care environments.
Call to Action

• Advocate for appropriate use of sex and gender terminology within your sphere of influence.

• NIH and FDA
  ➢ Health policies need to include specific language which mandates research design, analysis, and reporting by sex and gender.
  ➢ Periodic reporting by NIH and FDA of objective progress in advancing the health of women.

• NIH
  ➢ adopt a definition of “chronic debilitating diseases in women”
  ➢ allow tracking of funding by codifying this variable within applicable databases

• Crucial environments which require strategic and continuous engagement and advocacy
  • Congress
  • Pharmaceutical Industry
THANK YOU

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