When and How Should Sex Differences in Disease Susceptibility be Studied?

Kathryn Sandberg, PhD
Director, Center for the Study of Sex Differences in Health, Aging and Disease

Institute of Medicine
Forum on Neuroscience and Nervous System Disorders
San Francisco
March 8, 2010
| When Should Sex Differences in Disease Susceptibility be Studied? |   |
When Should Sex Differences in Disease Susceptibility be Studied?

- When sex differences exist in anatomy
Some functions of memory appear to be different in males and females. Higher rates of blood flow in certain portions of the brain are associated with increased memory of verbal tasks. In women, but not in men. Compared to men, women are better able to remember faces.

While there are essentially no disparities in general intelligence between the sexes, a UC Irvine study by Richard Haier’s and colleagues at UCI and the Univ of New Mexico found significant differences in brain areas where males and females manifest their intelligence. The study shows women having more white matter and men more gray matter related to intellectual skill, revealing that no single neuroanatomical structure determines general intelligence and that different types of brain designs are capable of producing equivalent intellectual performance.

This study may explain why women tend to excel at integrating and assimilating information from distributed gray-matter regions (eg language) whereas men tend to excel in tasks requiring more local processing (eg mathematics).

This more centralized intelligence processing in women is consistent with clinical findings that frontal brain injuries can be more detrimental to cognitive performance in women than men.

MRI pictures which have been converted into structural brain maps that correlated brain tissue volume with IQ
Sex differences in neuroanatomy

Significant differences in brain areas where intelligence is manifested, suggests no single neuroanatomical structure determines general intelligence.

Some functions of memory appear to be different in males and females. Higher rates of blood flow in certain portions of the brain are associated with increased memory of verbal tasks. In women, but not in men. Compared to men, women are better able to remember faces.

While there are essentially no disparities in general intelligence between the sexes, a UC Irvine study by Richard Haier’s and colleagues at UCI and the Univ of New Mexico found significant differences in brain areas where males and females manifest their intelligence. The study shows women having more white matter and men more gray matter related to intellectual skill, revealing that no single neuroanatomical structure determines general intelligence and that different types of brain designs are capable of producing equivalent intellectual performance.

This study may explain why women tend to excel at integrating and assimilating information from distributed gray-matter regions (eg language) whereas men tend to excel in tasks requiring more local processing (eg mathematics).

This more centralized intelligence processing in women is consistent with clinical findings that frontal brain injuries can be more detrimental to cognitive performance in women than men.

MRI pictures which have been converted into structural brain maps that correlated brain tissue volume with IQ.
Our brain is affected by SEX
When Should Sex Differences in Disease Susceptibility be Studied?

- When sex differences exist in anatomy
- When sex differences exist in physiology
Some functions of memory appear to be different in males and females. Higher rates of blood flow in certain portions of the brain are associated with increased memory of verbal tasks. In women, but not in men. Compared to men, women are better able to remember faces.

Composites of brain activity from 10 males (top row) and 10 females (bottom row) showing both anterior and posterior temporal lobe views when they underwent functional magnetic resonance imaging while listening to excerpts from a popular novel. The images reflect blood flow to the areas of the brain activated by the exercise. Image: IU School of Medicine Department of Radiology.
Sex differences in listening

Apparently, men do listen but with only one side of their brains, while women use both.

Some functions of memory appear to be different in males and females. Higher rates of blood flow in certain portions of the brain are associated with increased memory of verbal tasks. In women, but not in men. Compared to men, women are better able to remember faces.

Composites of brain activity from 10 males (top row) and 10 females (bottom row) showing both anterior and posterior temporal lobe views when they underwent functional magnetic resonance imaging while listening to excerpts from a popular novel. The images reflect blood flow to the areas of the brain activated by the exercise. Image: IU School of Medicine Department of Radiology.
Sex differences in navigation

Make a sharp left at the shoe store, then a right at the Winn Dixie, then another left at the Starbucks.

In a virtual reality maze with landmarks - men and women perform equally well in navigating to the exit; however, if you change the angles - women will outperform men and if you remove the landmarks men will outperform women, suggesting men and women use different mechanisms to navigate - men use compass directions and women use landmarks.
Sex differences in navigation

Imaging studies have revealed that while both men and women use the right hippocampus to figure out how to exit, men also use the left hippocampus. Women don’t use the left hippocampus - instead in addition to the right hippocampus, they invoke the right prefrontal cortex.

Imaging studies show that men activate a distributed system of different brain regions on both sides of the brain while performing a spatial task. Women, however, activated these regions on only the right side of the brain.
What are the implications of these functional brain differences in disease?
When Should Sex Differences in Disease Susceptibility be Studied?

- When sex differences exist in anatomy
- When sex differences exist in physiology
- When sex differences exist in incidence and age of disease onset
Number of Strokes in Men and Women across the Life Span
### When Should Sex Differences in Disease Susceptibility be Studied?

- When sex differences exist in anatomy
- When sex differences exist in physiology
- When sex differences exist in incidence and age of disease onset
- When sex differences exist in symptoms and diagnosis of disease
Sex differences in stroke symptoms

Symptoms in Common

- Sudden numbness or weakness of the face, arm or leg, especially on one side of the body
- Trouble speaking or understanding
- Difficulty seeing in one or both eyes
- Difficulty walking, dizziness or loss of balance or coordination
- Severe headache with no known cause

Other symptoms more women experience than men

- Change in mental status, mental confusion or unconsciousness
- Less brain stem symptoms
- Nausea
- Heart attack-like symptoms, including chest pain, shortness of breath and/or heart palpitations

Lisabeth et al., Stroke 2009
<table>
<thead>
<tr>
<th>Sex differences in type of stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ŷ Men have more lacunar and atherosclerotic strokes than women (68% vs 19%)</td>
</tr>
<tr>
<td>Ŷ Women have more cardioembolic strokes (30% vs 23%)</td>
</tr>
<tr>
<td>Caso et al., <em>Women’s Health</em> 2010</td>
</tr>
</tbody>
</table>
Approximately 2 million Americans live with schizophrenia
Symptoms in women more frequently involve depression and greater impairment of thought conceptualization
Whereas men display more apathy, paucity of speech, disturbance in cognitive function and social isolation

Apathy is defined as diminished motivation not attributable to diminished level of consciousness, cognitive impairment, or emotional distress.

Women also report more mood symptoms than men thus complicating diagnosis by making it difficult to differentiate schizophrenia from depression with psychotic features
Sex Differences in Disease Symptoms

John Forbes Nash, Jr.

Nobel Prize in economic sciences in 1994

John F. Nash, Jr. in his Nobel Prize Acceptance Speech 1994
In Stockholm
When Should Sex Differences in Disease Susceptibility be Studied?

- When sex differences exist in anatomy
- When sex differences exist in physiology
- When sex differences exist in incidence and age of disease onset
- When sex differences exist in symptoms and diagnosis of disease
- When sex differences exist in disease severity, progression and outcome
<table>
<thead>
<tr>
<th>Sex differences in treatment for stroke</th>
</tr>
</thead>
</table>
| Women admitted to hospitals while suffering stroke symptoms were 30% less likely to receive tissue plasminogen activator (tPA) than men experiencing such symptoms – **Why?**  
  Women frequently delay seeking treatment |
### Sex differences in outcome for stroke

More women were institutionalized than men and had worse functional status at 6 months after stroke
  
  Kapral et al., *Stroke* 2005

More women had lower functional recovery than men and poorer quality of life 3 months post-discharge, independently of age at stroke onset or other demographic or clinical characteristics
  
  Gargano et al., *Stroke* 2007

While short-term survival is the same, having survived stroke, women live longer
  
  Andersen et al., *J Stroke & Cardiovasc Disease*
Sex differences in drug efficacy

**Pain killers**

Aspirin is more effective than ibuprofen in women.

A recent study indicated that chronic aspirin therapy is not cardioprotective in women as it is in men, but aspirin did decrease the incidence of strokes in women.

---

Women have lower body weight and organ sizes and a higher percentage of body fat which can affect drug metabolism.

Diazepam, a muscle relaxant is often used to treat epilepsy and impairs the psychomotor skills in women more than men.

Verapamil and erythromycin are apparently more effective in women than men due to increased activity of the liver enzyme CYP3A4. CYP3A4 is responsible for metabolizing more than 50% of pharmaceutical drugs.

SSRI (selective seratonin reuptake inhibitors) used to treat depression appear to be maintained at higher blood concentrations in women than in men. Perhaps related to CYP liver enzymes CYP1A2 and CYP2C19.

Acetaminophen in inactivated nearly 50% more in women taking oral contraceptives compared with those who aren’t.

Women wake up from anesthesia faster than men and 3 times more women than men complain of being awake during surgery.
Sex differences in adverse drug effects

**Drug-induced arrhythmias**

Many drugs have been withdrawn by the FDA because of a higher incidence of drug-induced arrhythmias in women.

**FDA Request to remove Seldane from the market**

Seldane is terfenadine indicated for relief of symptoms associated with allergies.

For several years, the U.S. Food and Drug Administration has received reports that in certain people, Seldane (terfenadine) is associated with a potentially fatal heart condition, ventricular arrhythmia. Those at risk are people who have liver disease or take Seldane with certain antibiotic and antifungal drugs, such as erythromycin and ketoconazole. Eight deaths have been attributed to Seldane use.
Men die sooner than women from all the leading causes of death in the USA

Table 3: Sex-specific mortality rates and sex differentials for the twelve leading causes of death *
United States, 1980

<table>
<thead>
<tr>
<th>Cause</th>
<th>Age adjusted mortality rate</th>
<th>Sex ratio (M/F)</th>
<th>% death difference (M-F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accidents</td>
<td>41.9</td>
<td>0.79</td>
<td>7.2</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>17.3</td>
<td>0.91</td>
<td>8.4</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>26.1</td>
<td>0.89</td>
<td>17.2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>9.8</td>
<td>0.77</td>
<td>7.6</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10.2</td>
<td>0.89</td>
<td>9.2</td>
</tr>
<tr>
<td>Heart disease</td>
<td>18.3</td>
<td>0.50</td>
<td>3.5</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>17.1</td>
<td>0.79</td>
<td>9.2</td>
</tr>
<tr>
<td>Malignant neoplasms</td>
<td>165.5</td>
<td>0.41</td>
<td>56.3</td>
</tr>
<tr>
<td>Malignant neoplasms</td>
<td>109.3</td>
<td>0.51</td>
<td>56.3</td>
</tr>
<tr>
<td>Menstrual disorders</td>
<td>19.1</td>
<td>0.75</td>
<td>5.1</td>
</tr>
<tr>
<td>Neonatal deaths</td>
<td>11.3</td>
<td>0.79</td>
<td>3.5</td>
</tr>
<tr>
<td>Other cancer</td>
<td>29.8</td>
<td>1.00</td>
<td>18.6</td>
</tr>
<tr>
<td>Pulmonary and circulatory diseases</td>
<td>26.1</td>
<td>0.89</td>
<td>17.2</td>
</tr>
<tr>
<td>Pregnancy complications</td>
<td>9.8</td>
<td>0.77</td>
<td>7.6</td>
</tr>
<tr>
<td>Respiratory system</td>
<td>18.3</td>
<td>0.50</td>
<td>3.5</td>
</tr>
<tr>
<td>All causes</td>
<td>191.3</td>
<td>0.50</td>
<td>34.4</td>
</tr>
</tbody>
</table>

*Data based on cause of death
*Calculated from data from the National Center for Health Statistics, 1962-1980
For 10,000, death certification in the 1980 total US population

How Should Sex Differences in Disease Susceptibility be Studied?
How Should Sex Differences in Disease Susceptibility be Studied?

- Across the life span
The age of onset of asthma is earlier in men than women
How Should Sex Differences in Disease Susceptibility be Studied?

- Across the life span
- Experimental models
Sex differences in hormonal milieu
How Should Sex Differences in Disease Susceptibility be Studied?

- Across the life span
- Expand number of experimental models
  - Aging
    - Perimenopause & menopause
    - 4-vinylcyclohexene diepoxide (VCD)
    - 18 mo SHR
    - Fischer344/BN rat
Atresia of Ovarian Follicles
How Should Sex Differences in Disease Susceptibility be Studied?

- Across the life span
- Expand number of experimental models
  - Aging
    - Perimenopause & menopause
      - 4-vinylcyclohexene diepoxide (VCD)
      - 18 mo SHR
    - Fischer344/BN rat
  - Disease susceptibility
    - 12 month Dahl salt-sensitive female rat
How Should Sex Differences in Disease Susceptibility be Studied?

- Across the life span
- Expand number of experimental models
  - Aging
    - Perimenopause & menopause
    - 4-vinylcyclohexene diepoxide (VCD)
    - 18 mo SHR
    - Fischer344/BN rat
  - Disease susceptibility
    - 12 month Dahl salt-sensitive female rat
  - Sex chromosome dosage
    - FCG, XO
    - Escape from X-inactivation
Differences in the sex chromosomes

For those of you who are too young to know....
Four Core Genotype

Parents

Progeny

XX-female

XY-male

XY-female

XX-female

XY-male

XX-male
When and How Should Sex Differences in Disease Susceptibility be Studied?

When?
Always

How?
Across the life span and by developing and expanding upon our current experimental models