

Pain, Sex and Gender



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May 24, 2017

UCD Centre for Translational Pain Research

— Advancing Science, Changing Pain —

Agenda

- Sex and gender differences
- Research findings
- Epidemiology



Discover

THE MAGAZINE | BLOGS | HEALTH & MEDICINE | MIND & BRAIN | TECHNOLOGY | SPACE

BLOGS | D-brief | The Crux | Astrobeat | Body Horrors | Citizen Science Salon | Lovesick Cyborg | Neuroskeptic | Out There | Science Sushi | Seriously

TESTED, EFFECTIVE PROGRAM
BACK YOUR LIFE FROM PAIN

Over 200,000 in print!

Managing Pain Before It Manages You

Third Edition

On proven techniques to start, treat, and prevent pain with a wisely

Caudill, MD, PhD, MPH



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I recommend *Women and Pain*." —Christiane Northrup, M.D.

- Indications for:
- Back Pain
 - Osteoporosis
 - Migraines
 - Rheumatoid arthritis
- and much more!

Women AND PAIN

It Hurts and What You Can Do

Including Complementary and Holistic Remedies

MARK YOUNG, M.D., F.A.C.P.,
with KAREN BAAR, M.P.H.

Everything You Need to Know to Prevent, Treat, and Beat Back Pain

Strong Women Strong Backs



Miriam E. Nelson, Ph.D.
Friedman School of Nutrition Science and Policy, Tufts University
with Lawrence Lindner, M.A.

The Name Millions of Women Turn to for Trusted Health Advice

- Simple exercises that work
- Techniques to reduce pain and make your environment work for you
- Complementary therapies and medical options

The Crux

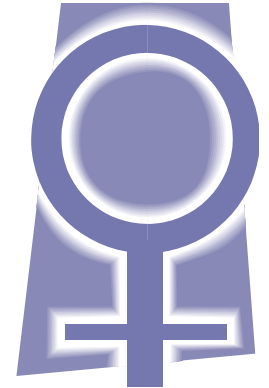
« Six Fish That Are Smarter Than We Give Them Credit For
With Gene Therapy We Could Direct Our Own Evolution »

Women Hurt More Than Men, Due to Both Biology and Bias

By Michael Brooks | March 6, 2015 2:35 pm

PETE EGOSCU
with Roger Gittines
authors of *Pain Eggs* and *Pain Free at Y*

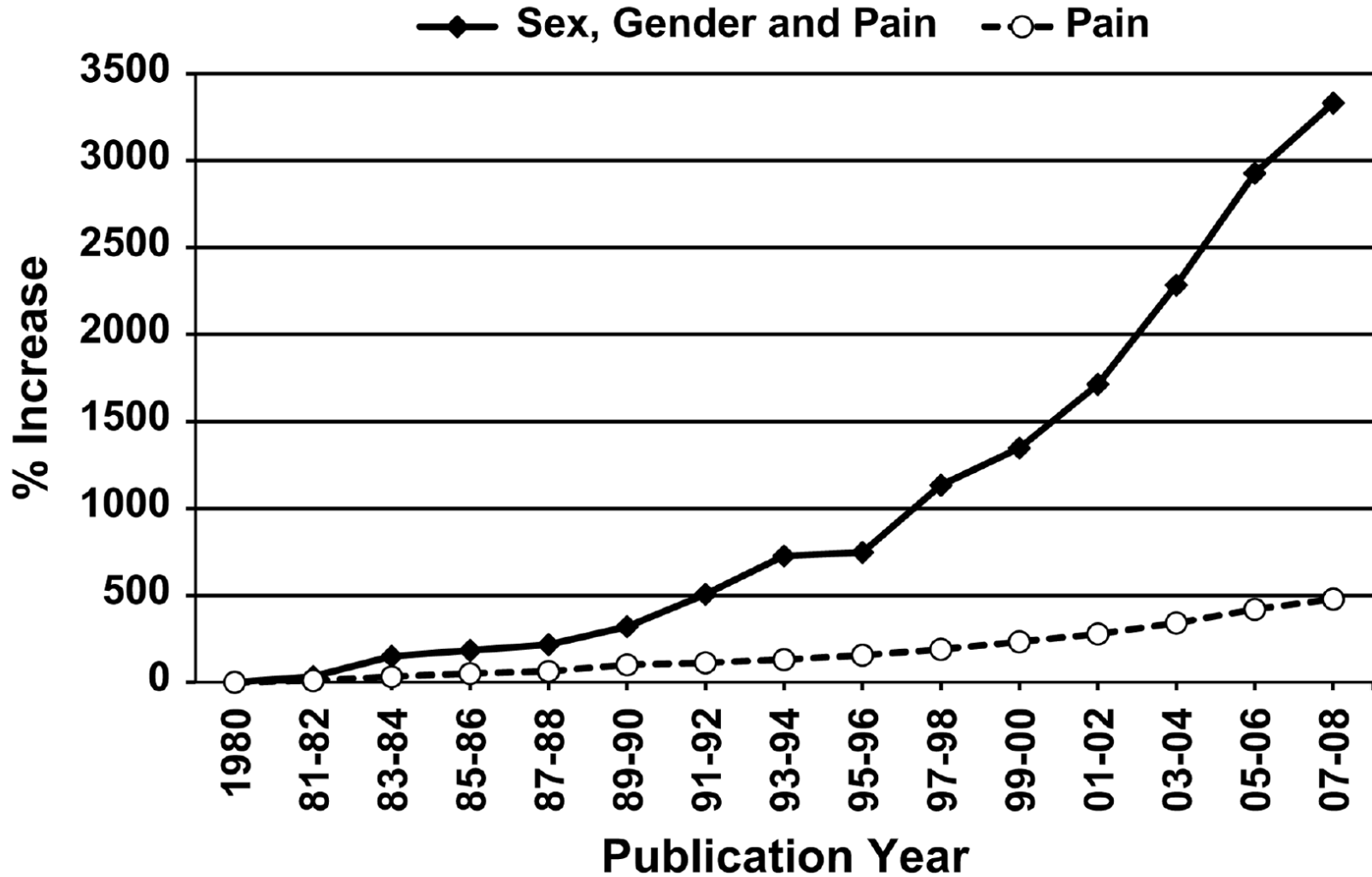
SEX: Determined by
chromosomes



GENDER: How one presents
oneself in society



Research Output



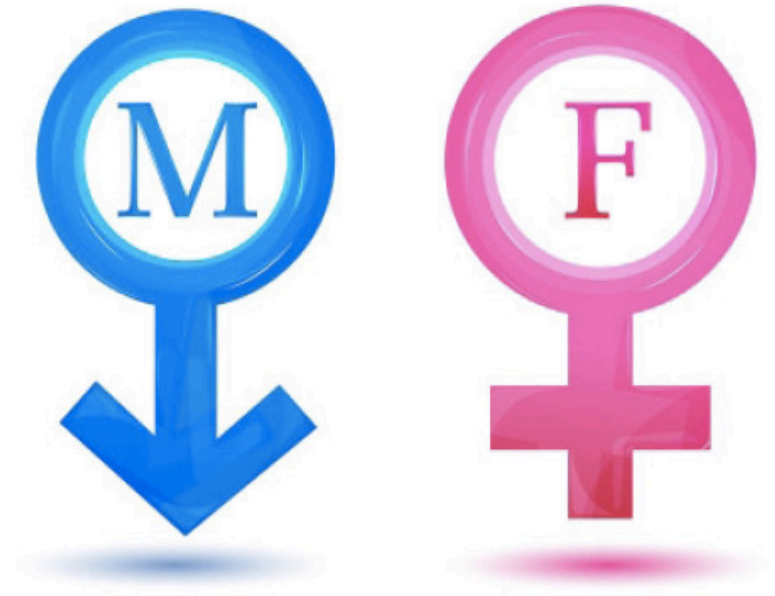
Men and Women Differ

1. Biological:

- Sex hormones
- Anatomical differences
- Genetics

2. Psychological:

- Emotion
- Coping strategies
- Health/pain behaviours
- Gender roles
- Use of healthcare services



Riley JL et al. *Pain* 1998;76:97–104

Fillingim RB et al. *J Pain* 2009;10:447–85

Gerdle B et al. *BMC Musculoskeletal Disorders* 2008;9:102

Men and Women are Different

- Pain is reported more frequently by women than by men
- Women report pain more than men in each of 10 different anatomical regions
- Women are significantly more likely to report chronic widespread pain
- Women are at greater risk of joint pain due to arthritis and of developing pain-related disability

Riley JL et al. *Pain* 1998;76:97–104

Fillingim RB et al. *J Pain* 2009;10:447–85

Gerdle B et al. *BMC Musculoskeletal Disorders* 2008;9:102



Men

are like Bluetooth:

he is connected to you
when you are nearby,
but searches for other devices
when you are away...



Women

are like Wi-Fi:

she sees all available devices
but connects to the strongest one...

Male Prevalence

- Cluster headache
- IHD
- Gout
- Pancreatitis
- Peptic ulcer disease
- Ankylosing spondylitis

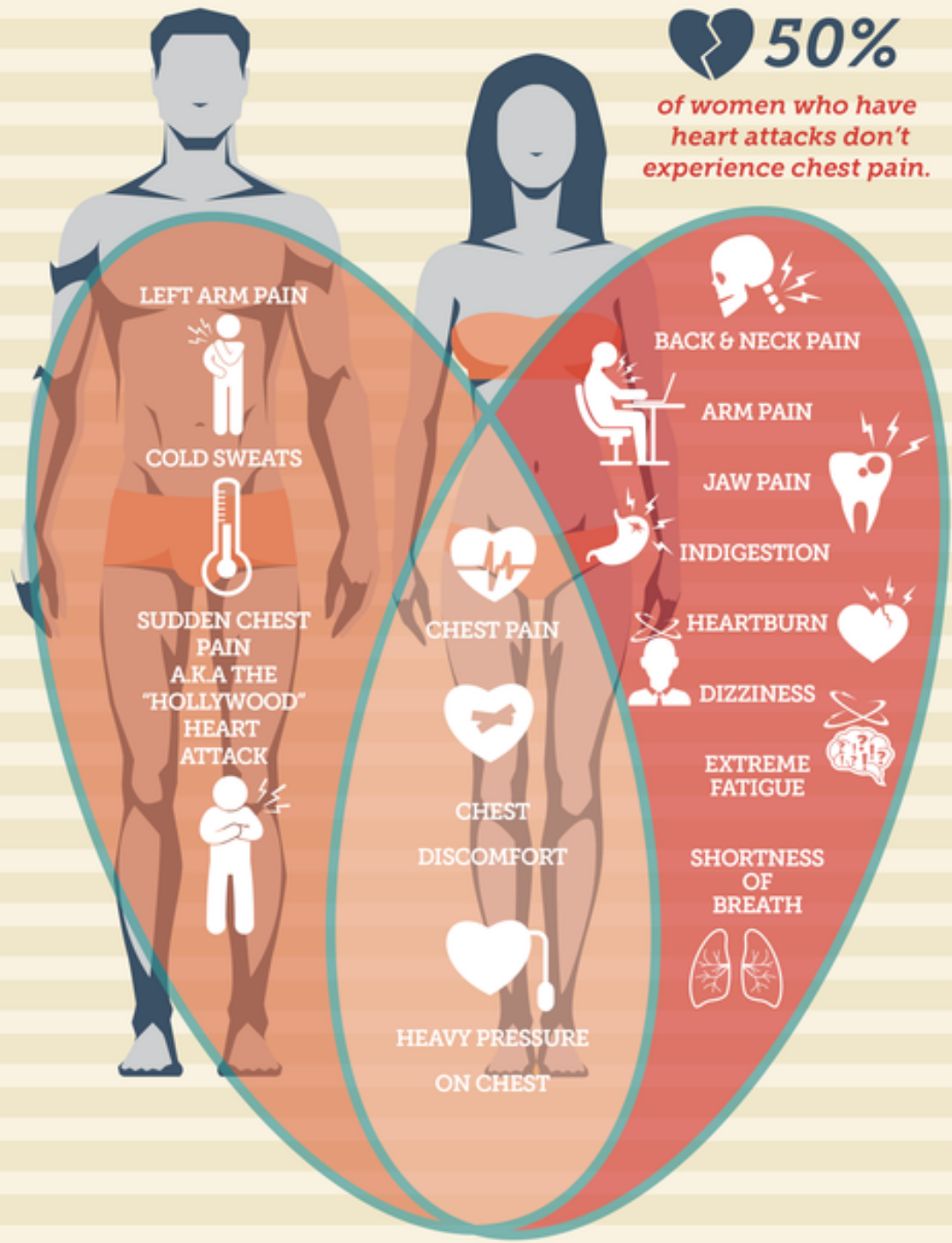
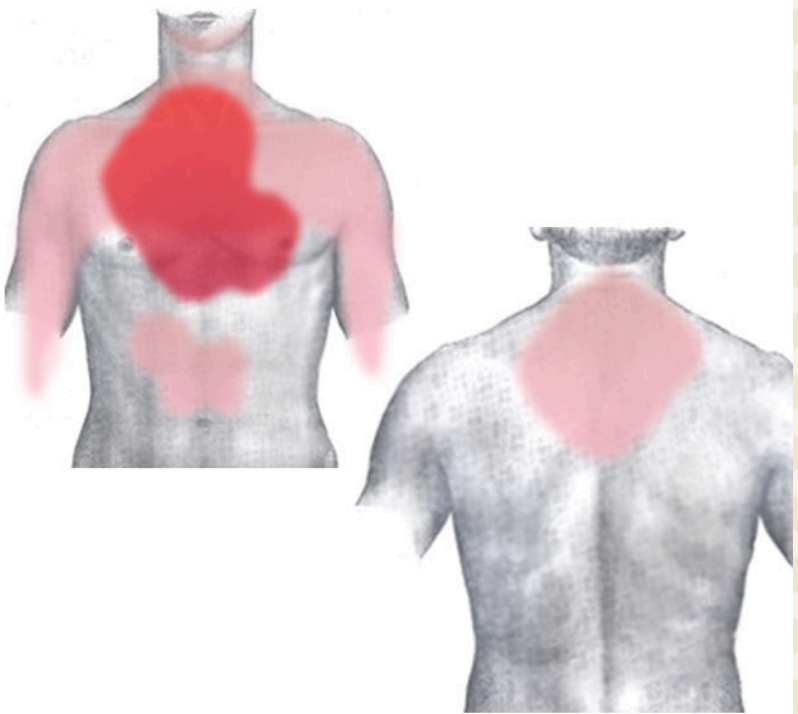


Female Prevalence



- Migraine headache
- RA, OA
- Fibromyalgia
- Carpal tunnel syndrome
- TMD
- Patellofemoral pain syndrome
- IBS
- deQuervain's tenosynovitis
- Chronic pelvic pain
- Interstitial cystitis

MI Symptoms



Healthcare Use by Sex

- Women tend to attend hospital at the same rate as men outside of childbearing age¹ (Broom, 2012)
- Men and women have broadly the same rates of depression when exposed to the same stressful non-gender specific situations² (Nazroo et al, 1997)

¹Broom D (2012) Gender and health. In: Germov J (ed) *Second Opinion: An Introduction to Health Sociology*. Melbourne: Oxford University Press

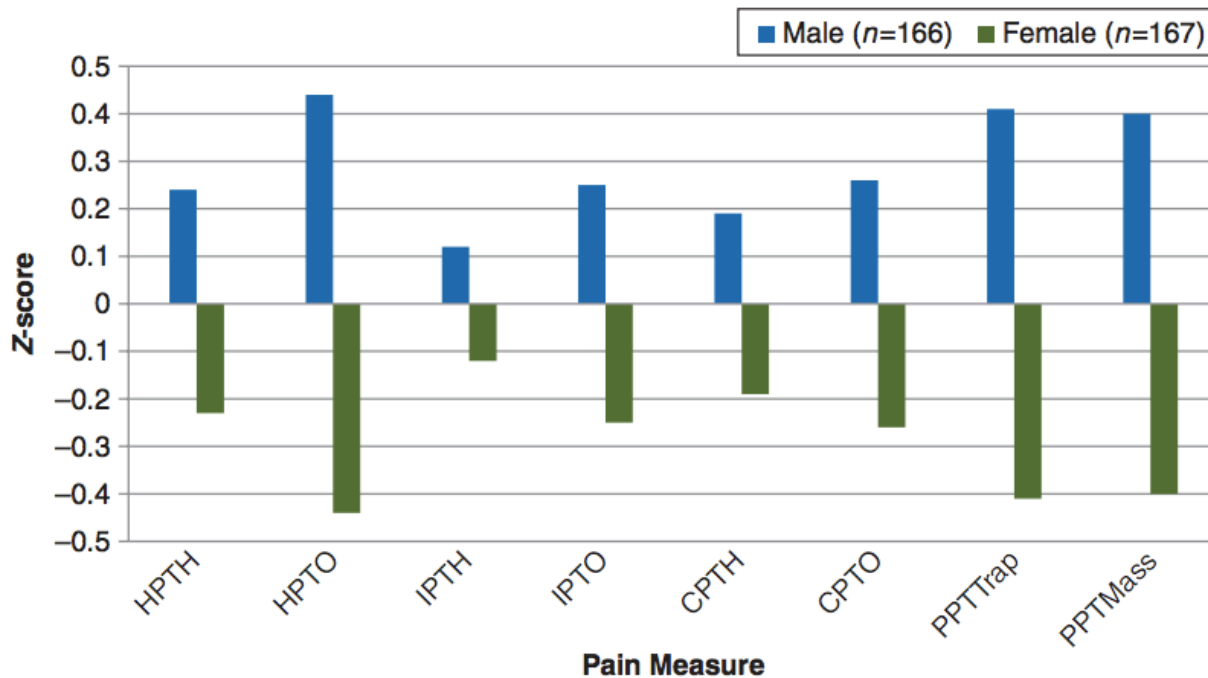
²Nazroo JY et al. *Psych Med* 1997;27(1):9-19

Research Model Bias



- 79% of all studies employed male subjects only
- 8% used female subjects only
- 4% of studies were explicitly designed to test if sex differences were present
- NIH requires pain studies in humans to include subjects of both sexes
- Non-human studies still largely ignore sex

Research Findings

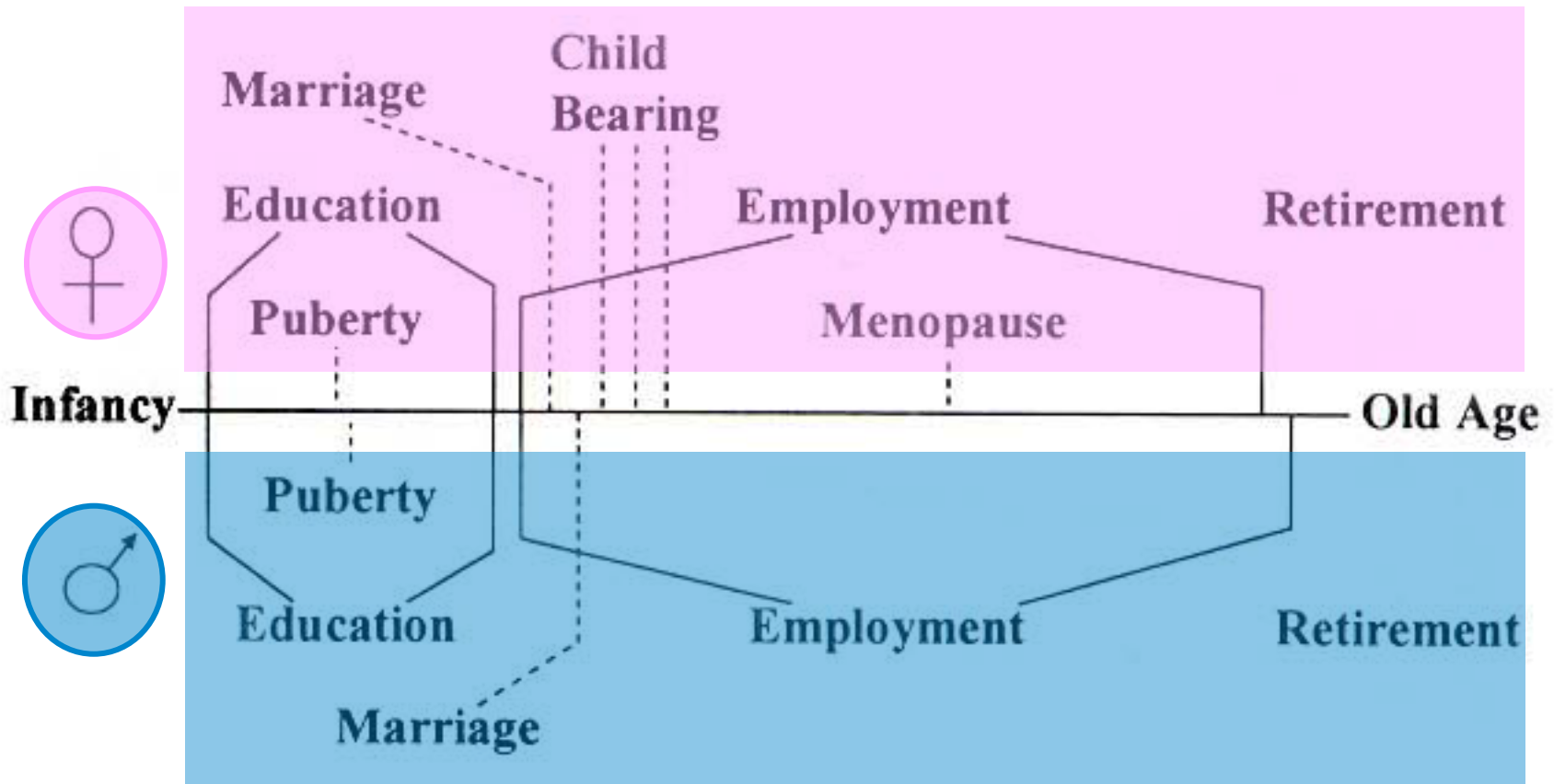


HPTH=heat pain threshold
HPTO=heat pain tolerance
IPTH=ischaemic pain threshold
IPTO=ischaemic pain tolerance
CPTH=cold pain threshold
CPTO=cold pain tolerance
PPTTrap=pressure pain threshold at the trapezius muscle
PPTMass=pressure pain threshold at the masseter

Genes and Proteins Implicated

1. Estrogen Receptor
2. Mu/Kappa/Delta opioid
(MOR, KOR, DOR)
receptors
3. GABA-A receptor
4. NMDA receptor
5. Melanocortin 1 receptor (MC1R)
6. Orphanin receptor
7. Protein Kinase A, C
8. G-protein-coupled inwardly rectifying potassium channel (GIRK2)
9. Acid-Sensing Ion Channel (ASIC)
10. Alpha2-adrenergic receptor

Life Cycle Differences Affect Pain



LeResche L. Gender differences in the epidemiology of chronic pain. In: Epidemiology of Pain, Crombie IK Ed: IASP Press, Seattle, 1999

Hormonal Influences on Pain

- No difference in TMJ disorders until puberty
- Symptom severity tends to vary during the menstrual cycle:
 - IBS
 - TMD
 - fibromyalgia
 - headache
- Migraine frequency declines and TMD pain is reduced during pregnancy
- Frequency of migraine increases as oestradiol levels fall post partum

Exogenous Hormone Effects

- Women on HRT have an increased risk for back pain and TMD
- Women report more severe orofacial pain when on HRT
- OCP use is related to an increased risk for carpal tunnel syndrome and TMD
- 30% of male-to-female subjects develop chronic pain (oestradiol and anti-androgens)
- 50% of female-to-male subjects report a significant improvement in chronic pain complaints (testosterone)

Peripheral Sex Hormone Effects

- Oestrogen effects on bone deposition and cartilage homeostasis
- Increased inflammatory response with oestrogens:
 - level of oestrogens
 - type of tissue which is inflamed
 - time course
 - time point at which oestrogen exposure occurs
- Oestrogen receptors found on primary sensory afferents
 - increase C-fibre activity
 - increase responsiveness when NMDA is injected

Endogenous Opioids

- Women have higher μ -opioid receptor binding in cortical and sub-cortical areas
- Men have greater μ -opioid receptor binding in other brain areas in response to experimental muscle pain
- Conditions characterised by high oestradiol levels are associated with reduced sensitivity to opioid agonists in experimental animal models

Zuheta JK et al. *J Neurosci* 2002;22:5100-5107

Fillingim RB , Ness TJ. *Neurosci Biobehav Rev* 2000;24:485-511

Dopamine

- Oestrogens and progestins have complex effects on dopamine turnover
- Sex differences in dopamine transporter function
- ?impact on sex differences in pain
- ?might explain the primary symptoms of fibromyalgia

Serotonin (5-HT)

- Complex effects on pain processing, depending on the receptor subtype and site of action
- Brain serotonergic function is modulated by ovarian hormones
- Centrally: associated with descending inhibition
- Peripherally: usually pro-nociceptive
- Greater brain 5-HT synthesis in female IBS patients may explain the visceral hypersensitivity

Gender Roles and Pain

1. Biological characteristics are often inferred from social characteristics, such as manner of dress
 2. Feminine gender norms accept pain as a normal part of life and are more permissive of pain expression
 3. Masculine gender norms dictate increased tolerance of pain
- Higher masculinity: increased mechanical pain thresholds in men but not in women¹
 - Greater masculinity relative to femininity: higher mechanical pain tolerance in both sexes¹

¹Otto MW, Dougher MJ. *Percept Mot Skills* 1985;61:383-390

Children

- Migraine headaches begin earlier in males but prevalence increases more rapidly in post-pubertal females
- Girls experience more recurrent headaches than boys
- Prevalence of chronic pain in Dutch children: 30% female to 20% male
- Chronic pain at multiple sites commoner in girls
- Sex differences appear to become evident or greater around puberty

Stewart WF et al. *Am J Epidemiol* 1991;134:1111-1120

Perquin CW et al. *Pain* 2000;87:51-58

LeResche L et al. *Pain* 2005;118:201-209

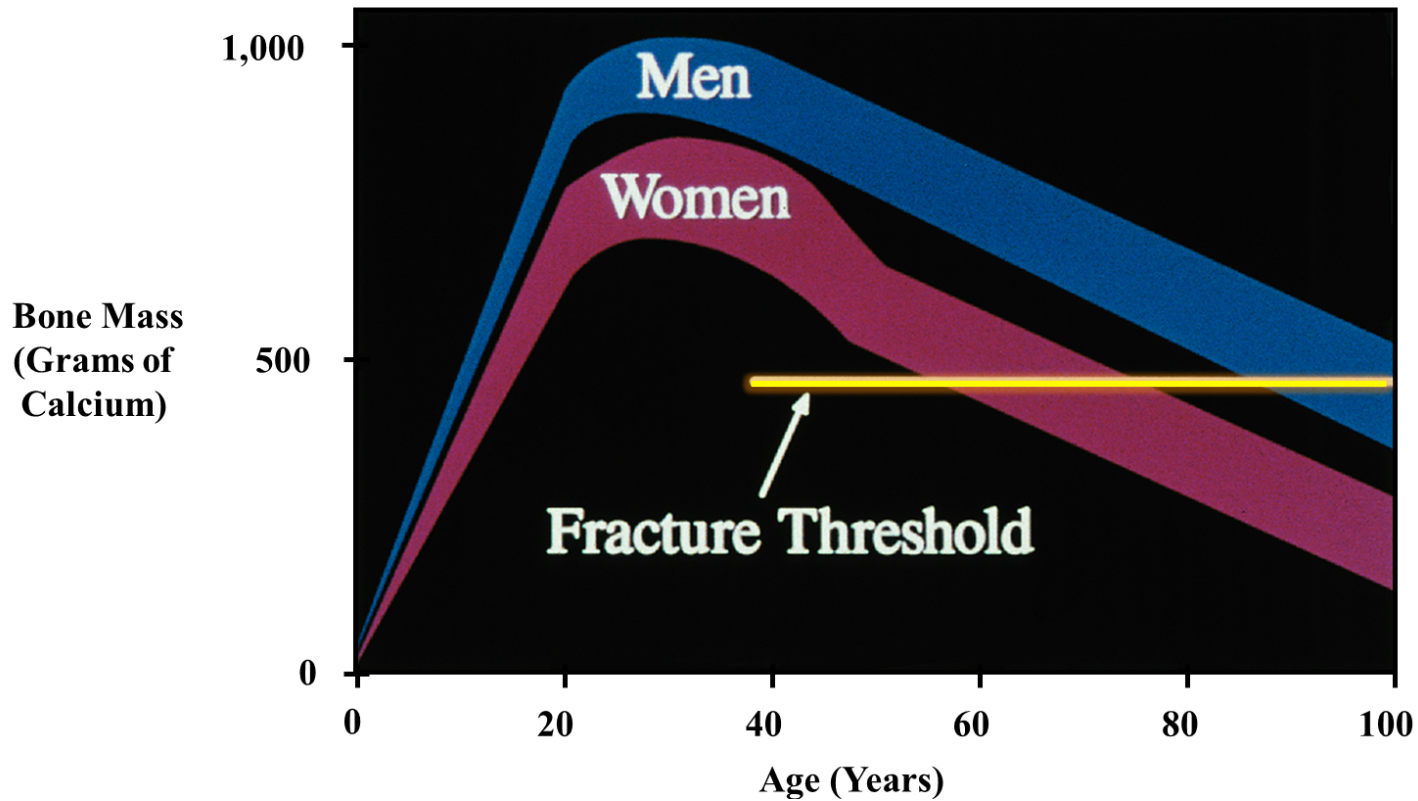
Summary of Research Findings

- Women display
 - greater sensitivity to multiple pain modalities compared with men
 - greater temporal summation of pain
- Men display greater conditioned pain modulation
- Women have
 - lower thresholds
 - greater ability to discriminate
 - higher pain ratings
 - lower tolerance of noxious stimuli

Bone Density and Muscle Mass

- Females have less muscle mass and different muscle fibre composition
- Testosterone and high levels of physical activity increase muscle mass
- Joint load is influenced by muscle strength and fatigue

Musculoskeletal Development



Lifetime Risk of Fracture

Fracture Site	Males (%)	Females (%)
Hip	6	17.5
Spine	5	15.6
Forearm	2.5	16
Any fracture	13	40

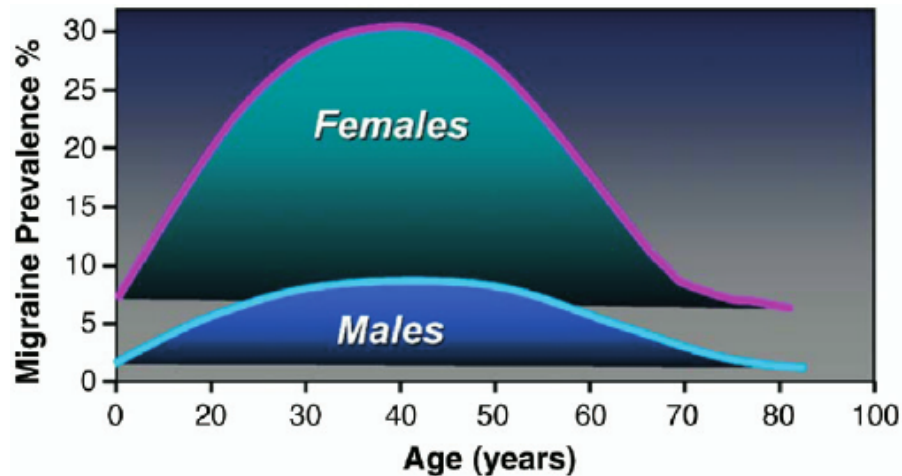
- Males more likely to sustain a second hip fracture
- Males more likely to experience severe disability

Opioid Studies

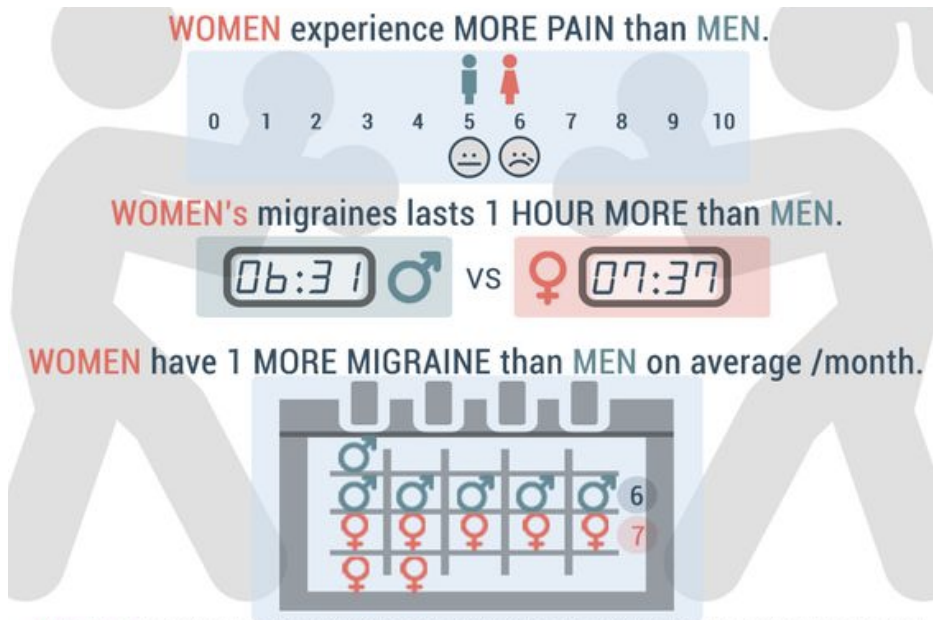
- Studies tend to assess opioid **consumption** rather than **pain relief**
 - may be influenced by factors other than analgesia (eg side-effects)
- Results were similar for experimental studies that directly assessed analgesic responses
 - suggesting greater morphine analgesia for women
- No sex-dependent effects were found for mixed action opioids across experimental studies
 - women exhibit greater analgesia than men in response to mixed action opioids

Migraine Headache

- At least 3 times commoner in women
- Pre-pubertal girls and boys have an approximately equal prevalence of migraine
- The lifetime prevalence of migraine increases to **18%** for women and **6%** for men after puberty



Migraine Headache



WOMEN have **LONGER, MORE PAINFUL & HIGHER FREQUENCIES** of migraines.
Hmm, seems like the **LADIES** have a **HIGHER** pain tolerance!

A larger proportion of **MEN** do **NOT** take **MEDICATION** to treat migraine pain



Cancer Pain

- In patients with inoperable lung cancer, women are more depressed at baseline than men
- One month after diagnosis, chest pain was reported as more intense by men, whereas women reported more intense pain in areas outside of the chest and arm/shoulder
- Women report greater pain in the abdomen before rectal cancer surgery, at discharge, and at 3 months after surgery
- Females are 20% more likely to have pain, fatigue and depression following cancer

Filligim RB et al. *J Pain* 2009;10(5):447–485

Reyes-Gibby CC et al. *J Pain Symptom Manage* 2006;32:118-128

Neuropathic Pain

- Females showed greater prevalence (6%) of chronic neuropathic pain compared with males (3%)¹
- Bouhassira found higher 3-month prevalence in females (8%) compared with males (6%)²
- Neither study reported sex differences in the effects of age, pain intensity, or depression
- It appears that women are at greater risk for neuropathic pain than men

¹Torrance N et al. *J Pain* 2006;7:281–289

²Bouhassira D et al. *Pain* 2008;136:380–387

Pain After Surgery

- Males likely to experience greater postoperative pain at rest and on movement¹
- Female adults and children more likely to report pain²
- No difference in pre- and post-TKR pain at 5 years³
- Females undergoing colonoscopy report greater pain than men
- Females report higher VAS after cholecystectomy
- Sex not associated with chronic pain 1 year after herniorrhaphy

¹Chia YY et al. *Can J Anaesth* 2002;49:249-255

²Mattila K et al *Anesth Analg* 2005;101:1643-1650

³Ritter MA et al. *J Arthroplasty* 2008;23:331-336

Sex Differences in Analgesia

- Most studies suggest minimal differences
- Females show greater increases in cold pain threshold and tolerance after morphine¹
- Ibuprofen gives greater analgesia after electrical pain in males²
- Lidocaine appears to give greater cutaneous analgesia in males

¹Pud D et al. *Neurosci Lett* 2005;380:209-213

²Walker JS et al.. *Anesth Analg* 1998;86:1257-1262

Nonpharmacological Treatment

- Men show decreased pain ratings after playing video games¹
- Women report lower cold pressor pain after treadmill exercise¹
- Pleasant smells reduce pain more in women than men²
- Conventional physiotherapy is more effective for men but intensive dynamic back exercises give better pain relief in women³

¹SternbergWF et al. *J Pain* 2001;2:65-74

²Marchand S et al. *Physiol Behav* 2002;76:251-256

³Hansen FR et al. *Spine* 1993;18:98-108

Conclusions

1. Prevalence of most common forms of pain is higher in females
2. Women display enhanced sensitivity to most forms of experimentally-induced types of pain
3. Men may exhibit greater diffuse noxious inhibitory control than women
 - DNIC might be predictive of clinical pain

Questions

1. Do research findings reflect gender-related response biases?
 - Men under-report pain
 - Women over-report pain
2. Do research findings reflect gender-based differences in endogenous pain modulation?
3. How significant are cognitive and affective variables?
 - Coping and catastrophising
 - Affective distress
 - Anxiety/depression

Research Possibilities

1. Sex differences and pain across the entire lifespan
2. Translation of laboratory findings to clinical studies
 - Specific gene associations
3. Human brain imaging and sex differences in reported pain
4. Role of psychological factors in gender and pain

Summary

- Chronic pain affects a higher proportion of women than men worldwide but women are less likely to receive treatment
- Women tend to have more recurrent, severe and long-lasting pain than men
- Many pain conditions are far more prevalent in women than in men
- Women's pain has a significant global impact
- The differences in pain modulation observed between the sexes may be more qualitative than quantitative

Thank You

S U C C E S S
F A I L U R E