UNIVERSITÀ
DEGLI STUDI
DI PADOVA

Medicina di genere e mantenimento dell'omeostasi del corpo umano

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Dipartimento di Scienze Chirurgiche Oncologiche e Gastroenterologiche

01. Gender Medicine

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Sex or Gender?

Sex or Gender?

SEX:

«The totality of characteristics of reproductive structure, functions, **phenotype**, and **genotype**, differentiating the male from the female organism.»

MeSH Database

Sex or Gender?

GENDER IDENTITY

«A **person's concept of self** as being male and masculine or female and feminine, or ambivalent, based in part on physical characteristics, parental responses, and psychological and social pressures. It is the internal experience of gender role.

Year introduced: 1991(1975).»

GENDER ROLE

«Social role encompassing a range of **behaviors and attitudes** that are considered acceptable based on perceived sex.

Year introduced: 2021»

MeSH Database

Gender Blindness and Gender Bias

GENDER BLINDNESS

Failure to identify or acknowledge differences on the basis of gender where they are significant

GENDER BIAS

Behavior that shows favoritism toward one gender over another

Rothchild, J. (2014). Gender Bias. In The Blackwell Encyclopedia of Sociology, G. Ritzer (Ed.). https://doi.org/10.1002/9781405165518.wbeosg011.pub2

Gender Blindness and Gender Bias

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

The Yentl Syndrome

Bernadine Healy, M.D.

Sex bias in the management of **coronary heart disease**

In *«Yentl, the Yeshiva boy»* from I. Singer, Yentl was a young woman who **had to dress and act like a boy** to be able to attend school and be educated in the Talmud

Healy B. The Yentl syndrome. N Engl J Med. 1991;325(4):274-276.
doi:10.1056/NEJM199107253250408

Why Gender Medicine?

Why Gender Medicine?

«Sex and gender-sensitive medicine is an **innovative approach to the practice of medicine** that postulates that biological **sex differences, gender identity, role, and relations** all **impact health and disease**, and that these differences may have **implications for prevention, screening, diagnosis, and treatment**.»

Oertelt-Prigione SaR-ZV. Sex and Gender Aspects in Clinical Medicine. Springer, London 2012

Why Gender Medicine?

«The ultimate goal of this field is to **learn from these differences** (or the absence thereof) and **improve care and treatment** of both men and Women»

Wagner AD, Oertelt-Prigione S, Adjei A, Buclin T, Cristina V, Csajka C, Coukos G, Dafni U, Dotto GP, Ducreux M, Fellay J, Haanen J, Hocquelet A, Klinge I, Lemmens V, Letsch A, Mauer M, Moehler M, Peters S, Özdemir BC.
Gender medicine and oncology: report and consensus of an ESMO workshop. Ann Oncol. 2019 Dec 1;30(12):1914-1924. doi: 10.1093/annonc/mdz414. PMID: 31613312.

Why Gender Medicine?

nature

www.nature.com/nature Vol 465 | Issue no. 7299 | 10 June 2010

Putting gender on the agenda

Biomedical research continues to use many more male subjects than females in both animal studies and human clinical trials. The unintended effect is to short-change women's health care.

«Differences in the **physiology** of males and females, and in their **response to disease**, have been recognized for decades in many species — not least *Homo sapiens*. […]»

«And yet, despite the obvious relevance of these sex differences to experimental outcomes, […] **male** research subjects continue to **dominate biomedical studies**.»

«[…] However justifiable these **imbalances** may be on a case-by-case basis, their cumulative effect is pernicious: medicine as it is currently applied to women is **less evidence-based** than that being applied to men.»

Gender Medicine: a Task for the third Millennium

Review > Clin Chem Lab Med. 2013 Apr;51(4):713-27. doi: 10.1515/cclm-2012-0849.

Gender medicine: a task for the third millennium

Giovannella Baggio [1], Alberto Corsini, Annarosa Floreani, Sandro Giannini, Vittorina Zagonel

Affiliations + expand

PMID: 23515103 DOI: 10.1515/cclm-2012-0849

«Gender medicine is a **neglected dimension** of medicine with respect to the study of **sex influences** on pathophysiology, clinical signs, prevention and therapy of diseases.

In the last 30 years too many epidemiological and clinical studies reported results in **only one sex**.»

Gender Medicine: a Task for the third Millennium

«Gender medicine is neither the medicine of gender-related diseases nor of diseases prevalent in a gender, mainly related to reproductive functions.

Gender-specific medicine needs to focus the attention and efforts of the scientific community on **understanding the differences of patho-physiology, clinical signs, prevention and treatment of diseases** equally represented in men and women.»

Baggio G, Corsini A, Floreani A, Giannini S, Zagonel V. Gender medicine: a task for the third millennium. Clin Chem Lab Med. 2013 Apr;51(4):713-27. doi: 10.1515/cclm-2012-0849. PMID: 23515103.

The Beginning of Gender Medicine …a Matter of the Heart!

Comparative Study > J Gend Specif Med. 2001;4(3):10-3, 20.

The effect of gender on age-related blood pressure changes and the prevalence of isolated systolic hypertension among older adults: data from NHANES III

D Martins [1], K Nelson, D Pan, N Tareen, K Norris

Affiliations + expand

PMID: 11605350

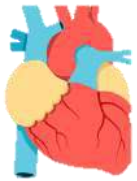
Review > J Clin Pharmacol. 2008 Nov;48(11):1350-5. doi: 10.1177/0091270008323754. Epub 2008 Aug 29.

Gender has a small but statistically significant effect on clearance of CYP3A substrate drugs

David J Greenblatt [1], Lisa L von Moltke

Affiliations + expand

PMID: 18757784 DOI: 10.1177/0091270008323754



«[…]Those papers were a starting point for good work in the cardiology field. However, **other fields of medicine did not improve** in the same way. »

Baggio G et al. Gender medicine: a task for the third millennium. Clin Chem Lab Med. 2013 Apr;51(4):713-27. doi: 10.1515/cclm-2012-0849. PMID: 23515103.

Clinical Trial > Atherosclerosis. 2001 Sep;158(1):183-93. doi: 10.1016/s0021-9150(01)00410-5.

Apolipoprotein E genotype affects plasma lipid response to atorvastatin in a gender specific manner

J Pedro-Botet [1], E J Schaefer, R G Bakker-Arkema, D M Black, E M Stein, D Corella, J M Ordovas

Affiliations + expand

PMID: 11500190 DOI: 10.1016/s0021-9150(01)00410-5

Clinical Trial > Lancet. 1992 Feb 8;339(8789):372. doi: 10.1016/0140-6736(92)91694-4.

Female sex as an important determinant of lisinopril-induced cough

I Os, B Bratland, B Dahlöf, K Gisholt, J O Syvertsen, S Tretli

PMID: 1346451 DOI: 10.1016/0140-6736(92)91694-4

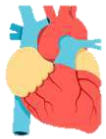
Gender Medicine…a Matter of the Heart! Twenty Years Later

Meta-Analysis > J Cardiovasc Electrophysiol. 2020 Dec;31(12):3176-3186. doi: 10.1111/jce.14758. Epub 2020 Oct 5.

Sex-based differences in procedural complications associated with atrial fibrillation catheter ablation: A systematic review and meta-analysis

Martin L Campbell [1], John Larson [1 2], Talha Farid [1 3], Stacy Westerman [1 3], Michael S Lloyd [1 3], Anand D Shah [1 3], Angel R Leon [1 3], Mikhael F El-Chami [1 3], Faisal M Merchant [1 3]

«Women experience significantly higher rates of AFCA complications[…] **More detailed studies are needed** to better define the mechanisms of increased risk in women and to identify **strategies for closing the sex gap** »



Meta-Analysis > Int J Cardiol. 2020 Mar 1;302:21-29. doi: 10.1016/j.ijcard.2019.12.014. Epub 2019 Dec 11.

Sex and gender-stratified risks of psychological factors for adverse clinical outcomes in patients with ischemic heart disease: A systematic review and meta-analysis

Veerle R Smaardijk [1], Angela H E M Maas [2], Paul Lodder [1], Willem J Kop [1], Paula M C Mommersteeg [3]

«Psychological factors are associated with MACE in samples with IHD in both women and men, with a small, but significant higher risk for men. […]**more research is needed** to better identify sex and gender **differences** in IHD.»

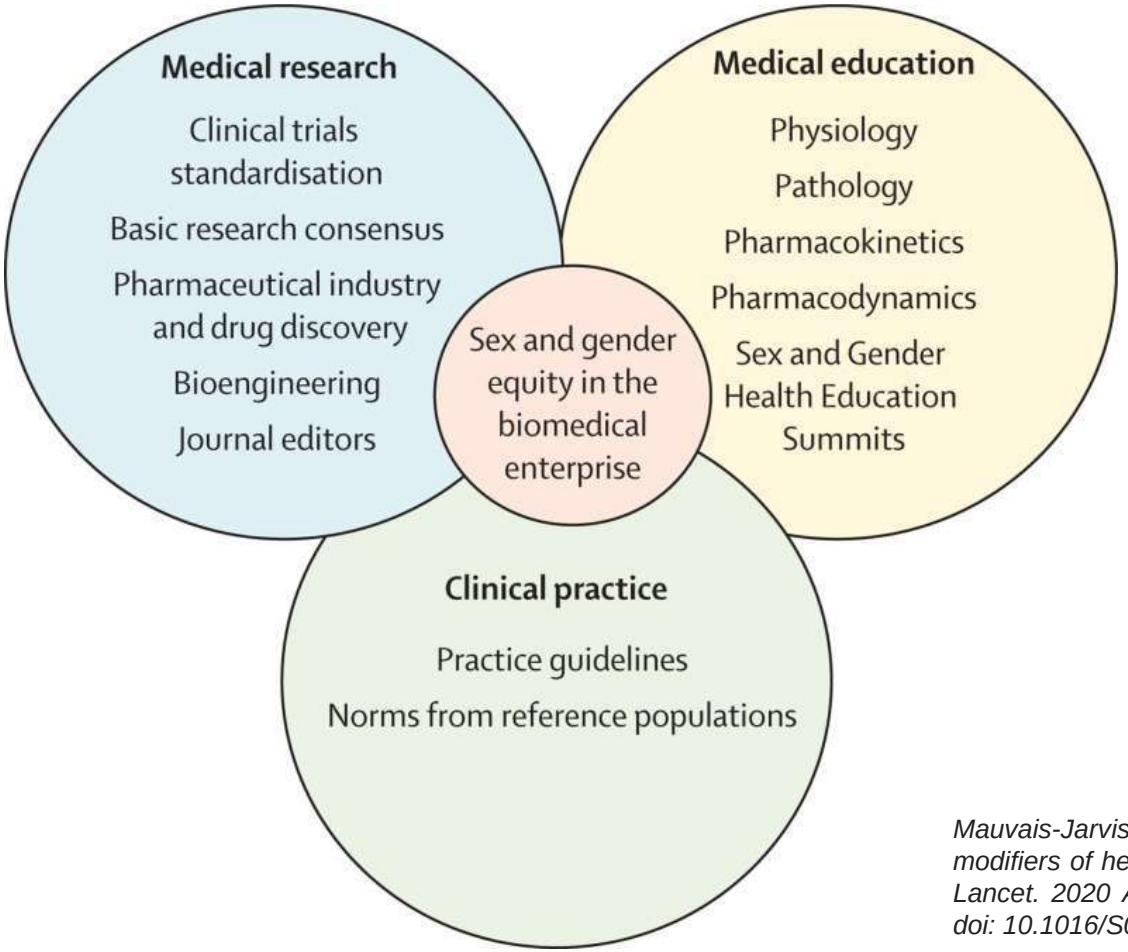
Professional Awareness

Intern Emerg Med. 2022 Aug;17(5):1395-1404. doi: 10.1007/s11739-022-02951-9. Epub 2022 May 23.

Awareness of sex and gender dimensions among physicians: the European federation of internal medicine assessment of gender differences in Europe (EFIM-IMAGINE) survey

« A total of 1323 European internists responded to the survey […]The majority (79%) recognized that sex and gender are not interchangeable terms, though a wide discrepancy exists on what clinicians think sex and gender concepts incorporate. Biological sex and sociocultural gender were recognized as determinants of health mainly in cardiovascular and autoimmune/rheumatic diseases. Up to 80% of respondents acknowledged the low participation of female individuals in trials and more than 60% the lack of sex-specific clinical guidelines. […] »

Professional Awareness

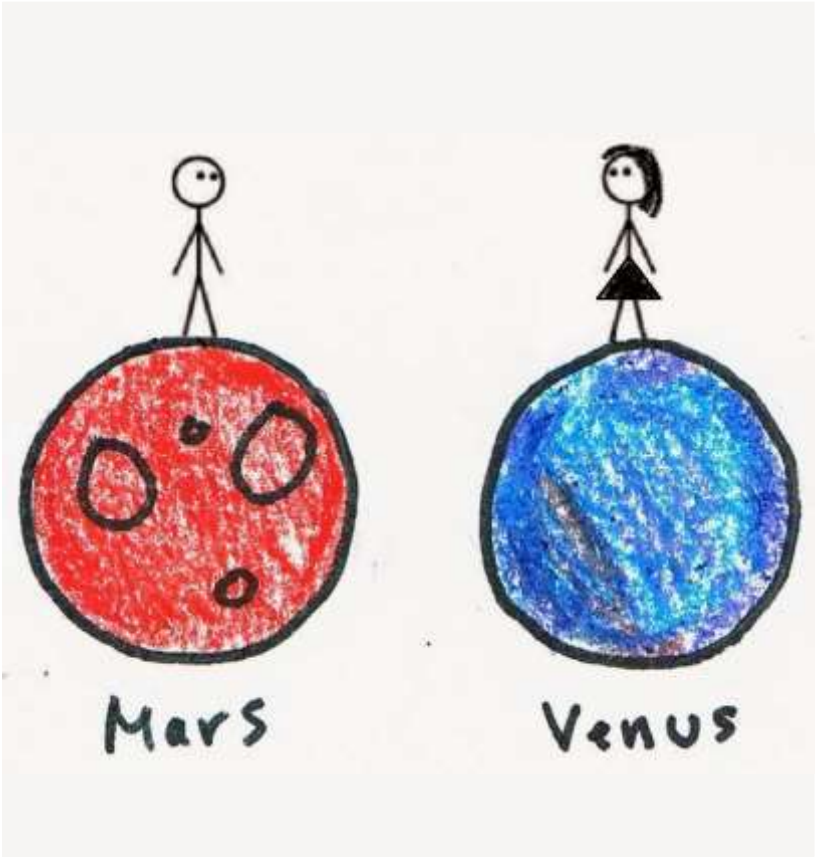


Mauvais-Jarvis F et Al. Sex and gender: modifiers of health, disease, and medicine. Lancet. 2020 Aug 22;396(10250):565-582. doi: 10.1016/S0140-6736(20)31561-0.

Summary of recommendations to promote sex and gender equity in the biomedical enterprise

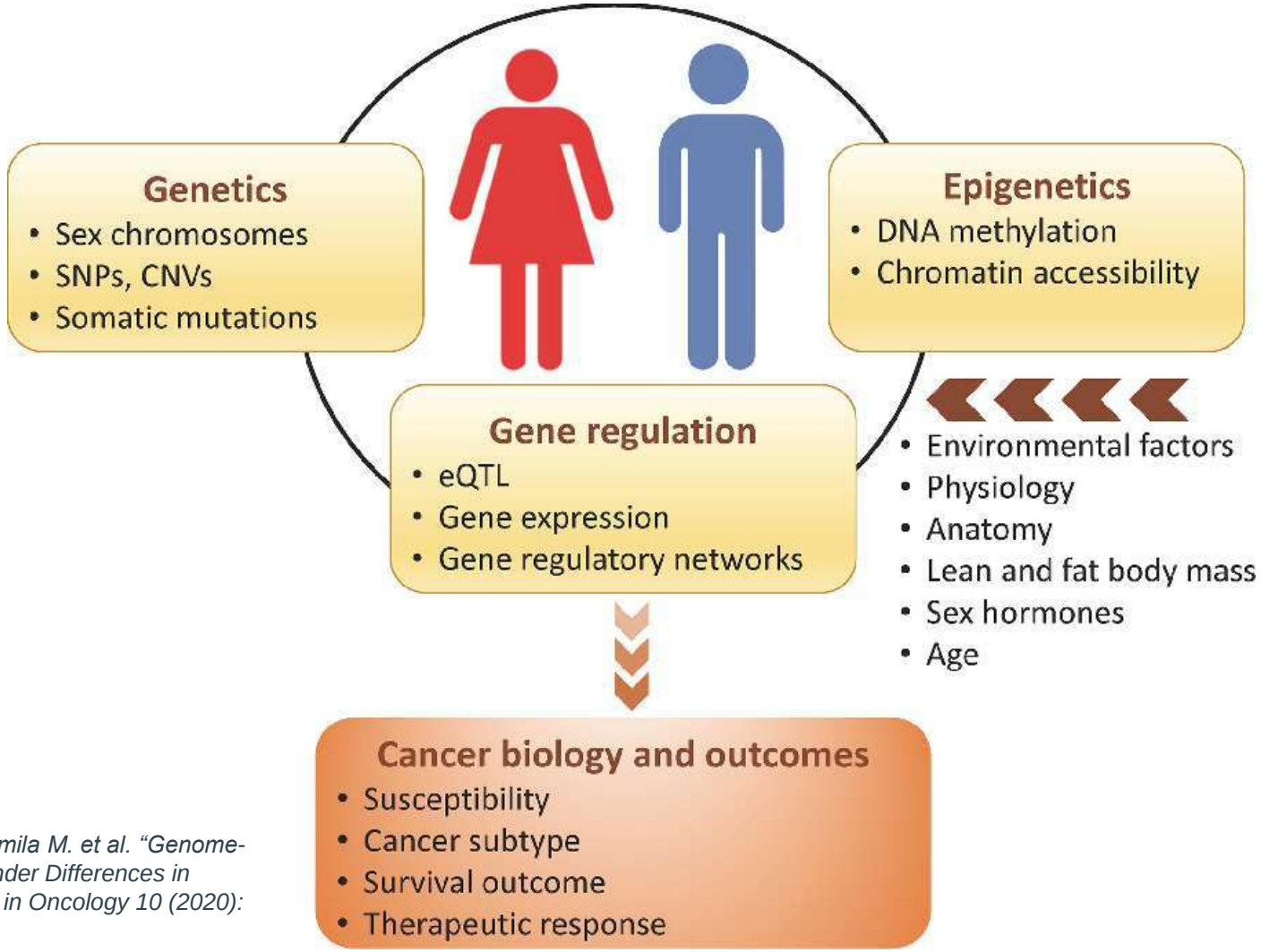
Gender Medicine: are we Different?

- Development, progression and clinical signs
- Epidemiology
- Adverse events associated with therapeutic treatments
- Response to treatments and nutrients
- Lifestyles
- Access to healthcare



https://www.epicentro.iss.it/en/gender-medicine/

Gender Medicine: why are we Different?



Lopes-Ramos, Camila M. et al. "Genome-Wide Sex and Gender Differences in Cancer." Frontiers in Oncology 10 (2020):

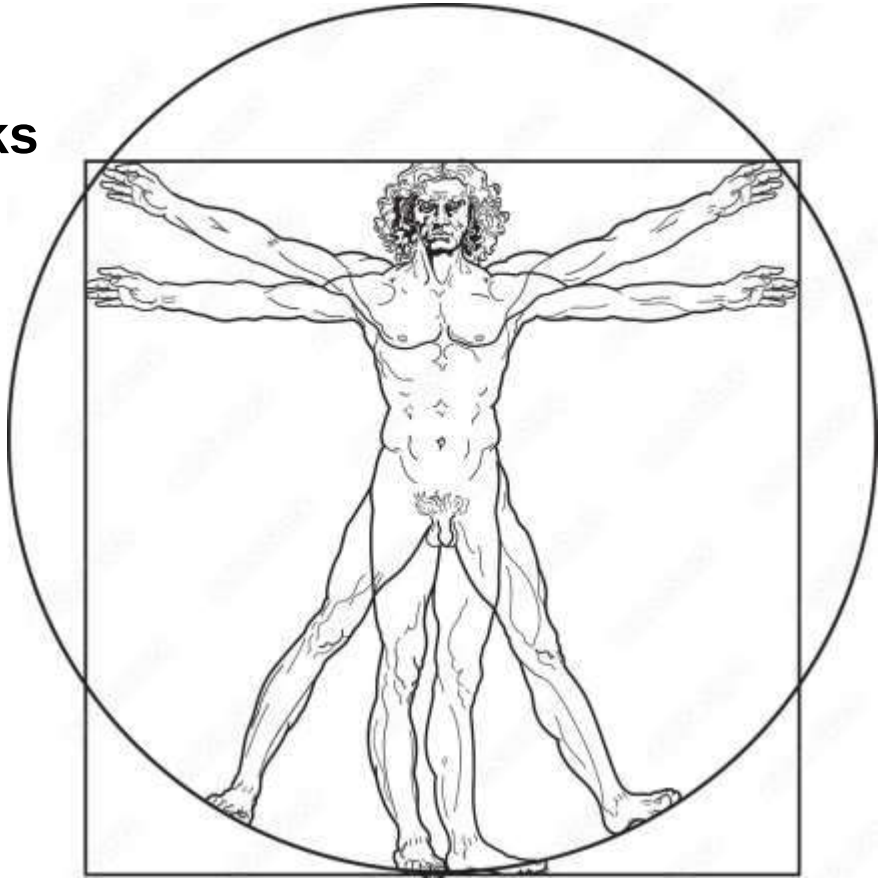
The Bias of the «Healthy Individual»

Sex & gender differences are NOT systematically adressed in textbooks

Limited view of:

- Mechanisms controlling organ and tissue function
- Diagnosis and care

SEX-BASED BIOLOGY



02. Sex and Gender Differences in Nutrition

Università degli Studi di Padova

Why are we Different in Nutrition?

- **Biology**
- **Environment**
- **Role and relations**
- **Gender identity**

Differences in Nutrition

«Until the last decade of the 20th century, **research on women** has been **neglected**, and the **results obtained in men** have been directly **translated to women** in both the **medicine** and **nutrition** fields. Consequently, **most modern guidelines** are based on **studies** predominantly **conducted on men**.»

Marino M, et al., Nutrition and human health from a sex-gender perspective. Mol Aspects Med. 2011;32(1):1-70. doi:10.1016/j.mam.2011.02.001

Differences in Nutrition

SEX-GENDER DIFFERENCES are the result of **multifactorial inputs**:

- gene repertoires
- sex steroid hormones
- environmental factors

Differences in Nutrition: Genes

Genetic Mechanisms

Sry, other genes

- Testes development
- Epinephrine synthesis: influence on BP, stress response, Na and K kidney excretion

Enzymes for

- oxidative stress
- cell survival
- Apoptosis
- fat distribution

Epigenetic Mechanisms

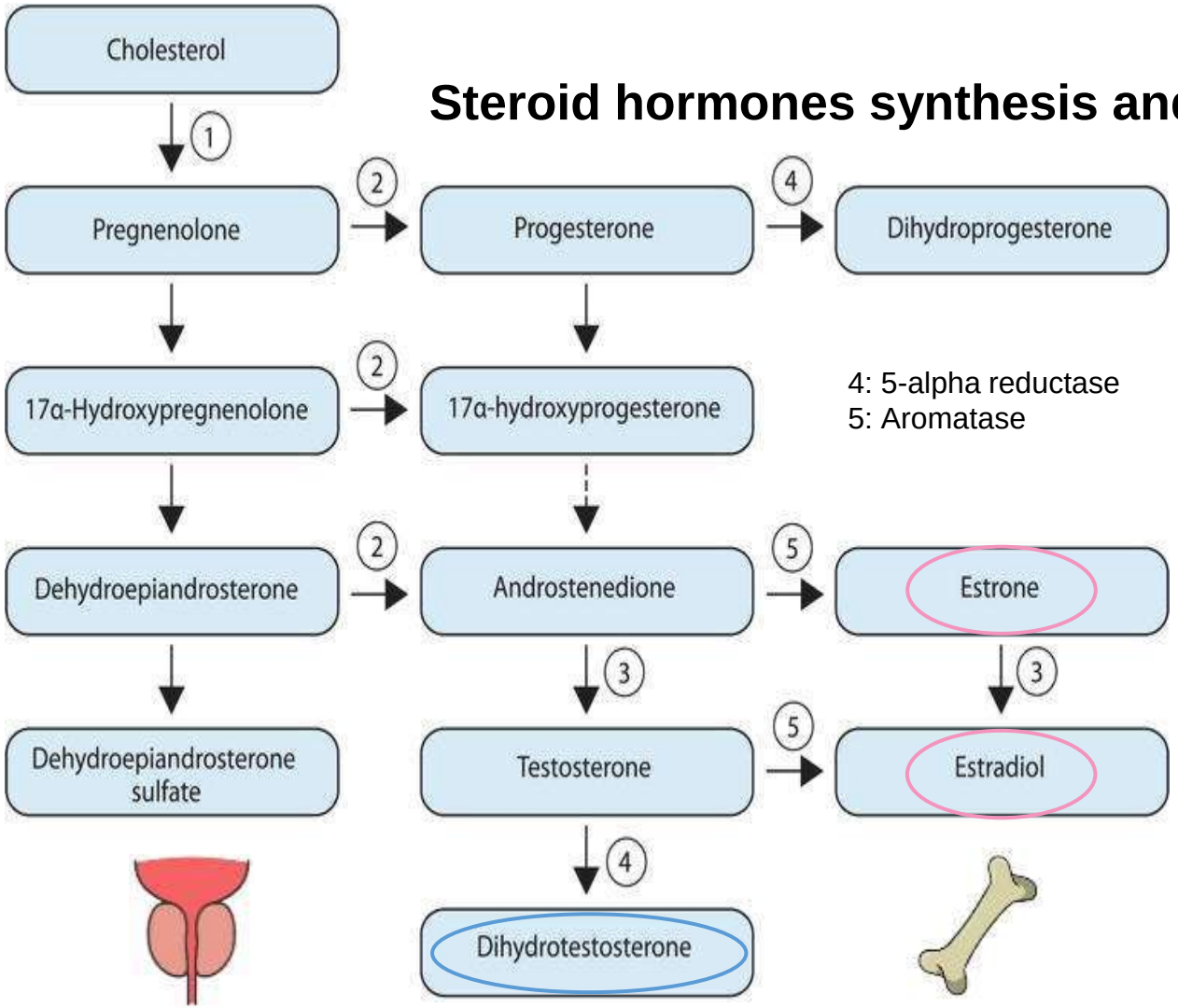
DNA methilation

- Embryogenesis
- Imprinting
- X-chromosome inactivation

Hormones regulation

Estrogens regulate DNA methylation through ER

Differences in Nutrition: Steroid Hormones

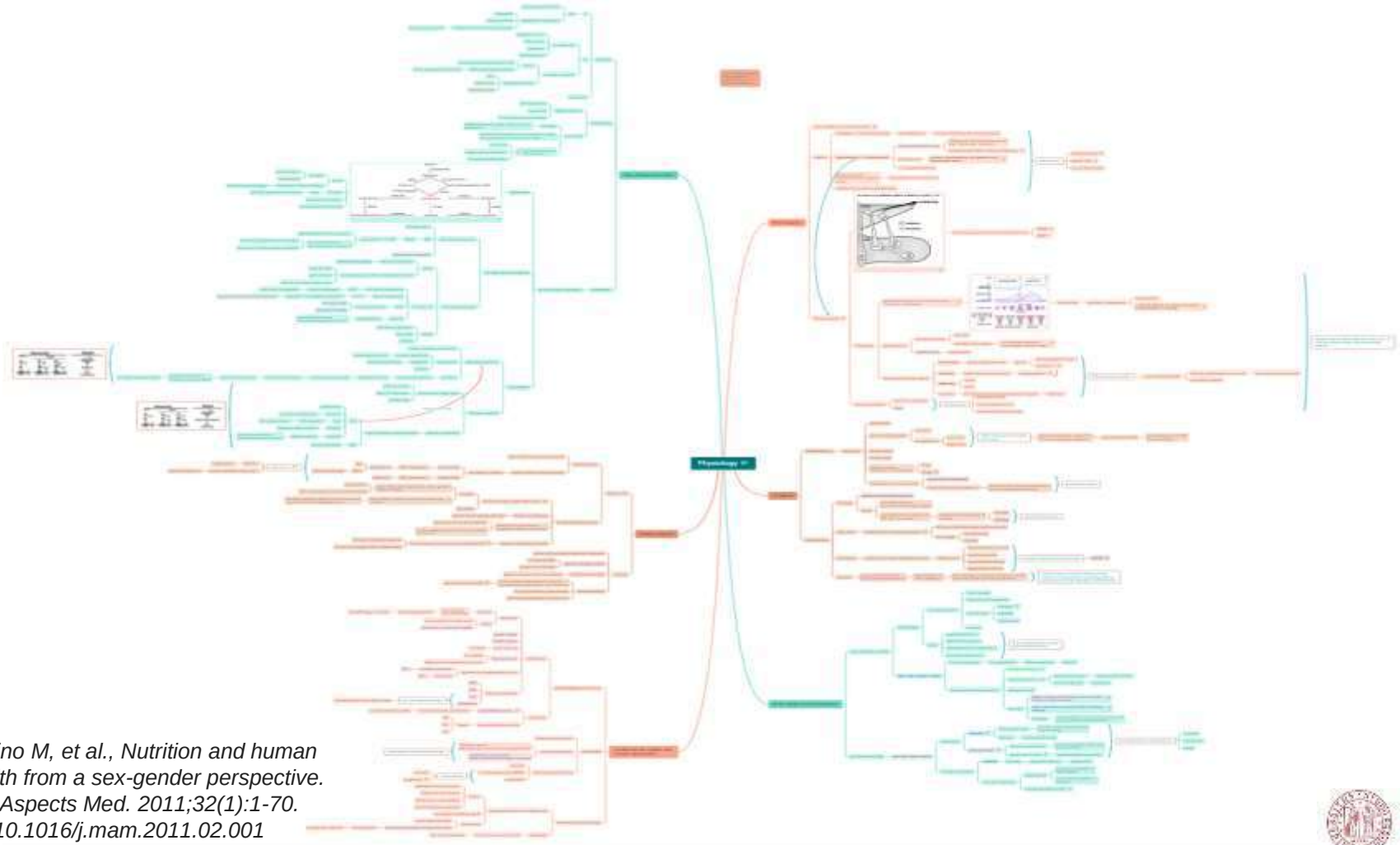


Receptors are also present in **non-reproductive tissues** (heart, bone, skeletal muscle, vasculature, liver, immune system, brain)

The complexities of gonadal steroid hormone metabolism and local variation are still not well understood

Delchev S. Cellular and Molecular Mechanisms of the Effects of Sex Hormones on the Nervous System (2018) DOI: 10.5772/intechopen.71140

Sex-Gender Differences in Physiology: how Complex Could it Be?



Marino M, et al., Nutrition and human health from a sex-gender perspective. Mol Aspects Med. 2011;32(1):1-70. doi:10.1016/j.mam.2011.02.001

Gender Differences Expression

How do gender differences express themselves in Nutrition?

Gender Differences Expression

DIFFERENCES of male and female body **FUNCTIONING:**

- food intake regulation
- bioavailability and metabolism
- distribution
- cardiovascular system and energy expenditure
- impact of food components on the risk of developing diseases

Food Intake

Peripheral regulation

Central regulation

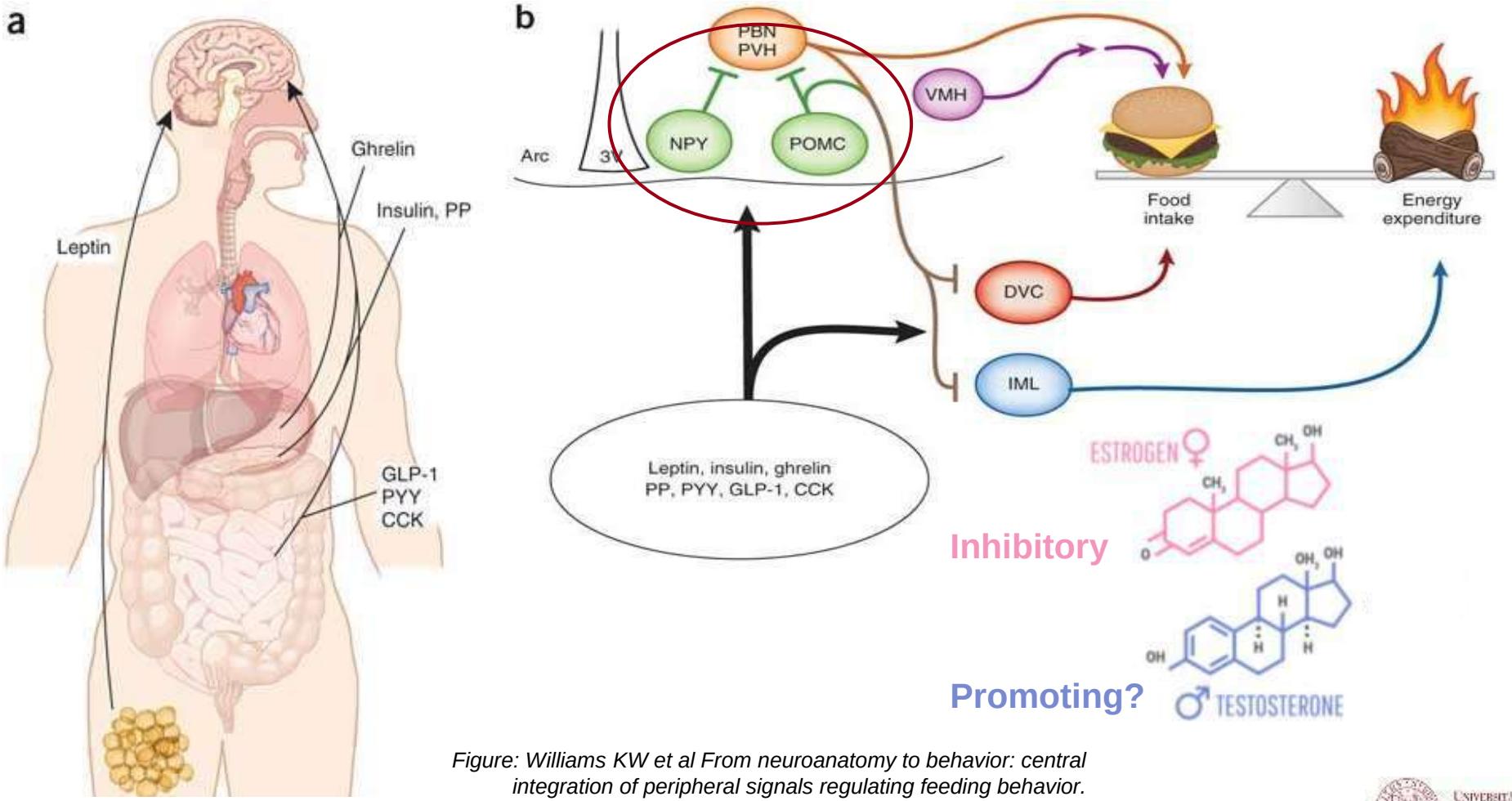
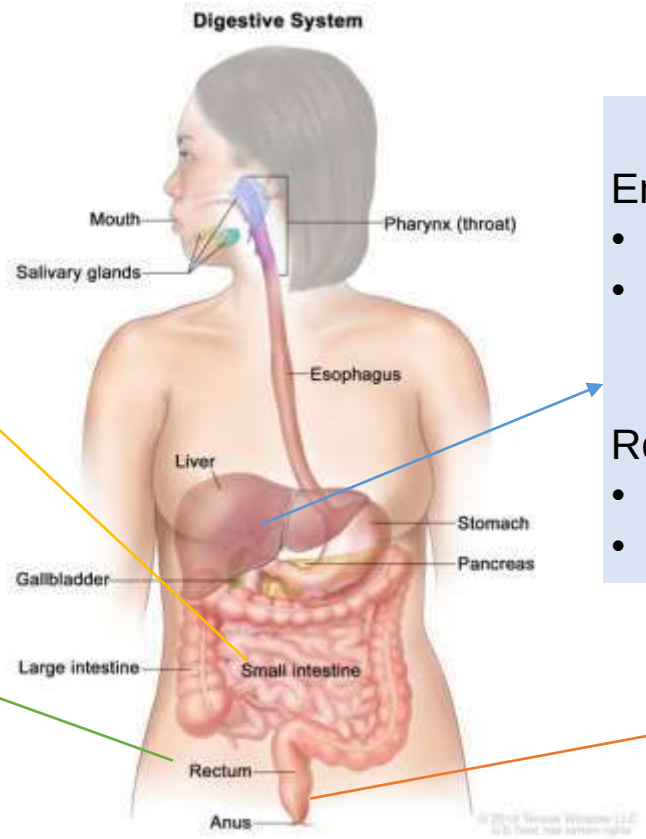


Figure: Williams KW et al From neuroanatomy to behavior: central integration of peripheral signals regulating feeding behavior. Nat Neurosci. 2012;15(10):1350-1355. doi:10.1038/nn.3217

Nutrients Bioavailability

Absorption
Gastric pH
Gastric emptying time
GI blood flow
Surface area



Metabolism
Enzymes:
- Alcohol dehydrogenase
- Cytochromes (CYP3A4, CYP2D6)

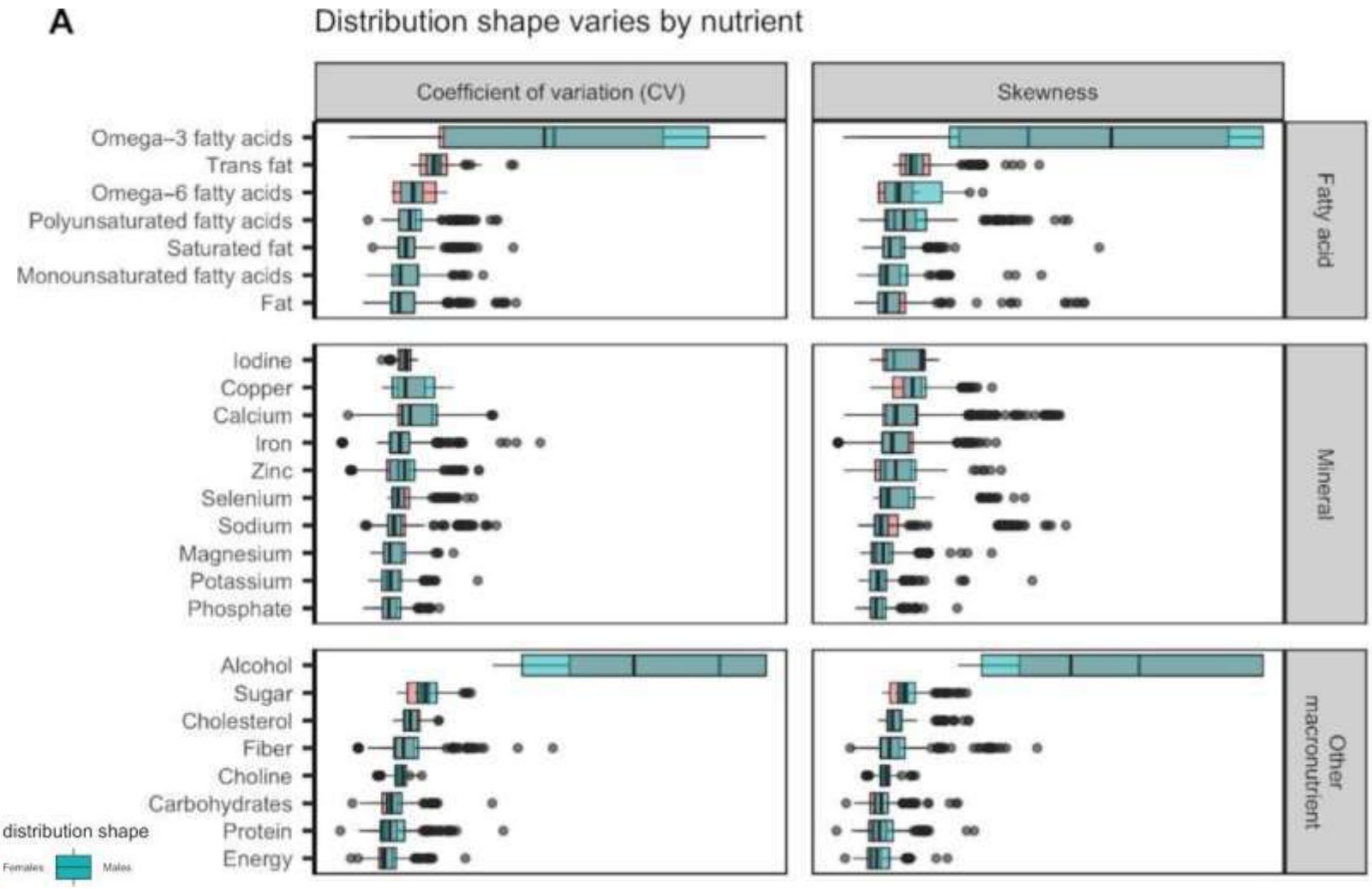
Receptors:
- Androstane
- Pregnane X

Distribution
P-glycoprotein (P-gp)

Elimination

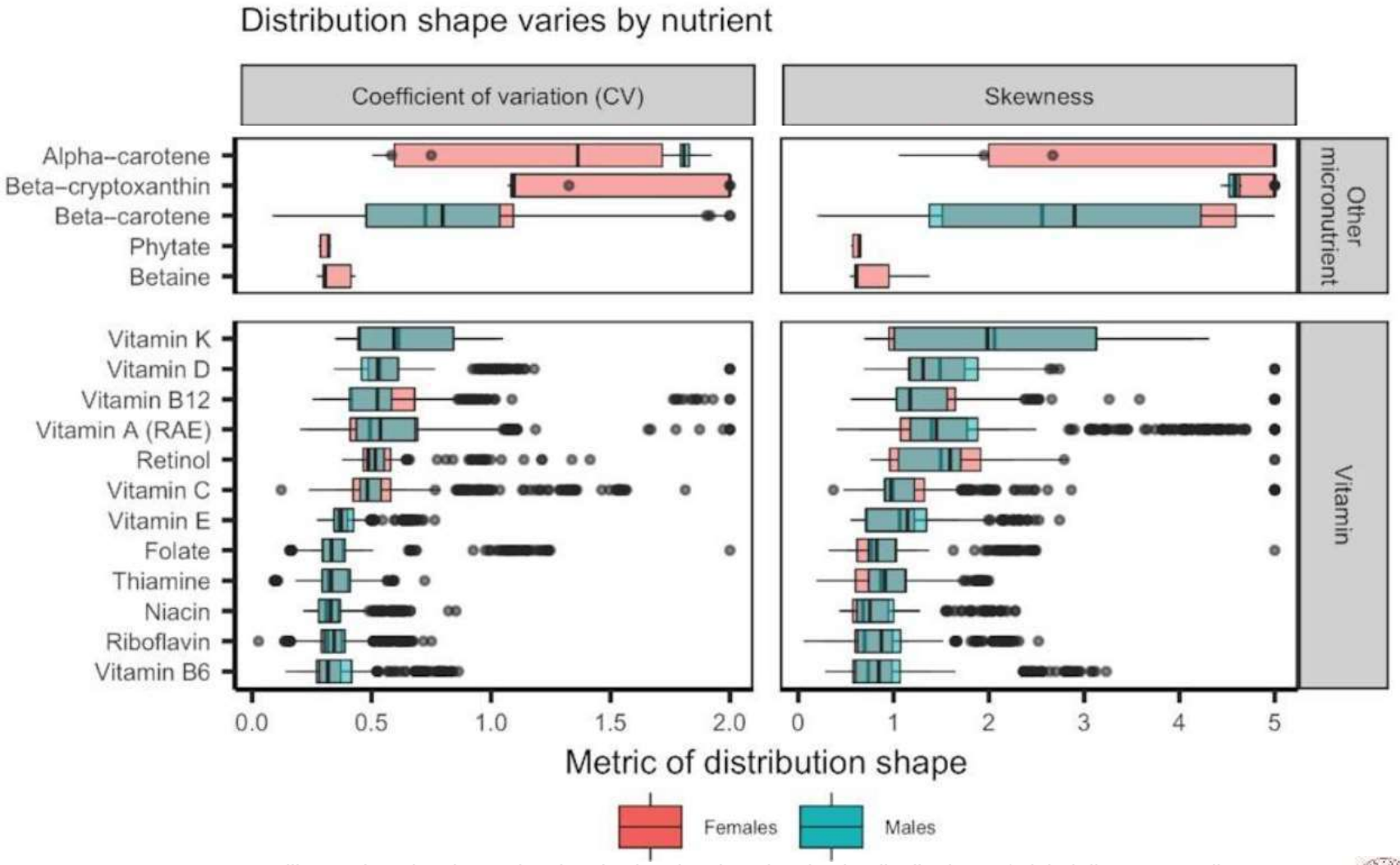
Influenced by
Autonomous Nervous System
Sex hormones

Nutrient Intake Distribution



Passarelli S et al. Estimating national and subnational nutrient intake distributions of global diets. Am J Clin Nutr. 2022 Aug 4;116(2):551-560. doi: 10.1093/ajcn/nqac108. PMID: 35687422; PMCID: PMC9348991.

Nutrient Intake Distribution



Passarelli S et al. Estimating national and subnational nutrient intake distributions of global diets. Am J Clin Nutr. 2022 Aug 4;116(2):551-560. doi: 10.1093/ajcn/nqac108. PMID: 35687422; PMCID: PMC9348991.

Lean Body Mass

Bone mass

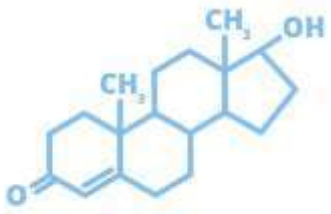
Skeletal muscle mass

Sex differences

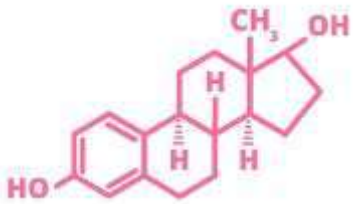
- Bone strenght
- Biomechanical responses
- Mineral mass
- Turnover
- Trabecular microstructure
- Aging modifications

Synthesis/breakdown balance

- Hormones
- Feeding/fasting
- Aging
- Diseases
- Exercise



Influenced by sex hormones



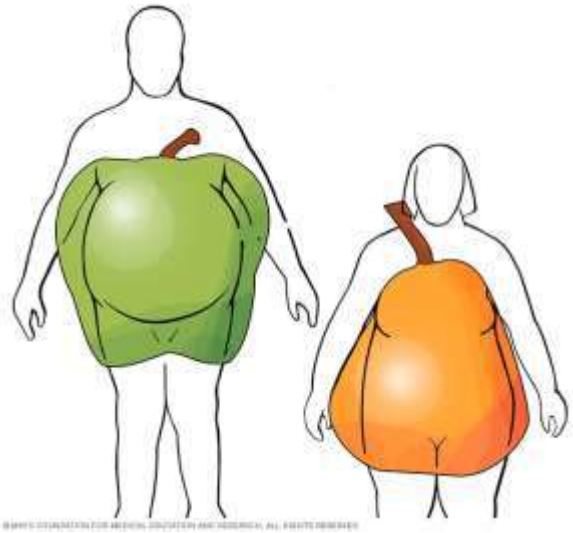
Fat Body Mass

Visceral

♂

Rapid mobilization

For specific intermittent activities (e.g. hunting)



Subcutaneous

♀

Constant mobilization

For chronic metabolic challenges (e.g. gestation)

Estrogen Regulation

Fat distribution

Lower **lipoprotein lipase** activity

⌄

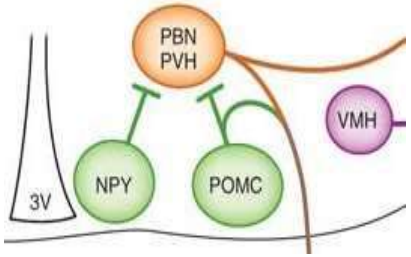
selective reduction in visceral adiposity

Body weight

Estrogen **deficiency**

⌄

orexigenic peptides activity in the hypothalamus



Figures: Williams KW et al. From neuroanatomy to behavior: central integration of peripheral signals regulating feeding behavior. Nat Neurosci. 2012;15(10):1350-1355. doi:10.1038/nn.3217

Nutrient Distribution

Volume distribution

Lipophilic agents

Fatty acids, polyphenols, lipophilic vitamins

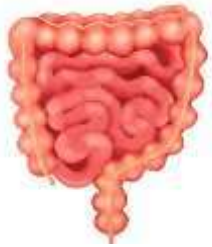
Hydrophilic agents

Carbs, proteins, hydrophilic vitamins

♀ ♂

Correlated to **body fat**

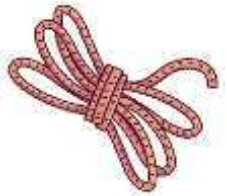
Postprandial response



Splancnic hyperhemia

Sex differences in **arterial blood flow** and **BP** response

Protein binding



Albumin
Alpha-1 acid glycoprotein
Alpha-globulin

Influenced by **estrogens** and **pregnancy**

The Impact of Cardiovascular System

- ♂ Heart size (15-30% larger)
- ♂ Blood vessels
- ♂ Cardiac output (CO)
- ♂ Blood pressure (BP, 3-5 mmHg higher)
- ♀ Heart rate (HR, 3-5 bpm higher, but not in utero)

- **Blood composition**: Pre-menopausal women
  → **antiatherogenic blood profile**
- **Response to cardiovascular stress:**
  - ♂ Vascular resistance → Blood pressure +
  - ♀ HR → Cardiac output +

Influenced by Autonomic Nervous System

Sympathetic
Parasympathetic

Energy Expenditure

Energy expenditure: the amount of energy an individual uses to maintain essential body functions and as a result of a physical activity

Heaney, J. (2013). Energy: Expenditure, Intake, Lack of. In: Gellman, M.D., Turner, J.R. (eds) Encyclopedia of Behavioral Medicine. Springer, New York, NY. https://doi.org/10.1007/978-1-4419-1005-9_454

the ‘‘average woman’’ works at a higher percentage of her exercise capacity than the ‘‘average man.’’

Energy Expenditure

Maximal oxigen uptake
(VO2 max)

3.5 L/min

Greater speed
Higher muscle strenght
Longer limbs

2 L/min

Greater endurance
Higher fat metabolism

Higher HR, body temperature, stress, fatigue

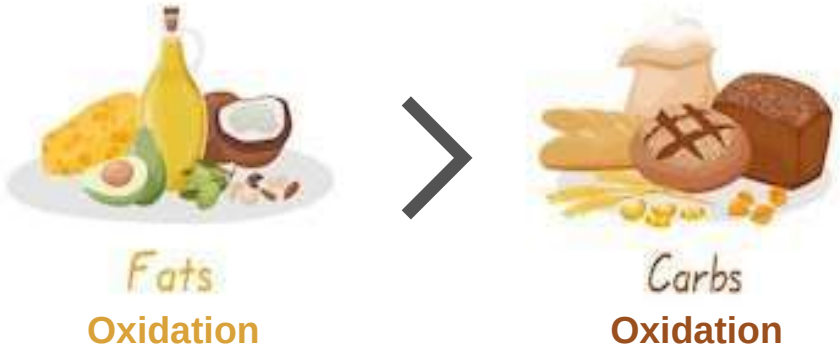
More injuries and **less tolerance of stressful moments**

Estrogen regulation of skeletal muscle mass and muscle remodeling

More **fatigue-resistant** and **faster-recovering** muscles

Fat and Exercise in Women

Women use more **fat-derived energy** during exercise than men



"Women may need to increase their dietary energy intake (and percentage derived from carbohydrates) for **four days before** a sporting event in order to compensate muscle glycogen concentrations"

Tarnopolsky MA, Ruby BC. Sex differences in carbohydrate metabolism. Curr Opin Clin Nutr Metab Care. 2001;4(6):521-526. doi:10.1097/00075197-200111000-00010

Nutritional Behaviour

Food choice is dependent on a wide spectrum of factors:
biological needs, psychological, emotional, economic and social issues

Sex Differences in Nutritional Behaviour

Men

- Fatty meals with a strong taste
- Directed by the pleasure of consumption
- Furtively eating of sweet
- More dietary supplements
- More frequent fast food visits

Women

- Trust in healthy nutrition
- Greater engagement in body weight control
- Tendency to eat in a group
- Tendency to eat in stressful situations
- Frustration due to nutritional behaviors
- Social pressure
- Attempts to reduce eating-related pleasure.

Grzymisławska M et al. Do nutritional behaviors depend on biological sex and cultural gender? Adv Clin Exp Med. 2020 Jan;29(1):165-172. doi: 10.17219/acem/111817. PMID: 32017478.

Female Nutrition

IRON	Exclusively brestfed infants, menstruating, pregnant and lactating women
VIT. B6	Reproductive-aged women using hormonal contraceptive agents
MAGNESIUM	Menstruating and premenopausal women, PPI users, those with altered glucose metabolism
FOLATE	Before and during early gestation
CHOLINE	During pregnancy and early life, across life course
VIT. B12	Pregnant, vegan and vegetarian women, those with IBD, older adults
IODINE	Pregnant women
ZINC	Across life course, older adults, nursing home residents, diuretics users
VIT. D & CALCIUM	Adolescents, adults, postmenopausal women

Bailey RL et al. Sex Differences Across the Life Course: A Focus On Unique Nutritional and Health Considerations among Women. J Nutr. 2022 Jul 6;152(7):1597-1610. doi: 10.1093/jn/nxac059. PMID: 35294009; PMCID: PMC9258555.

Nutrition in Frail and Elderly Population

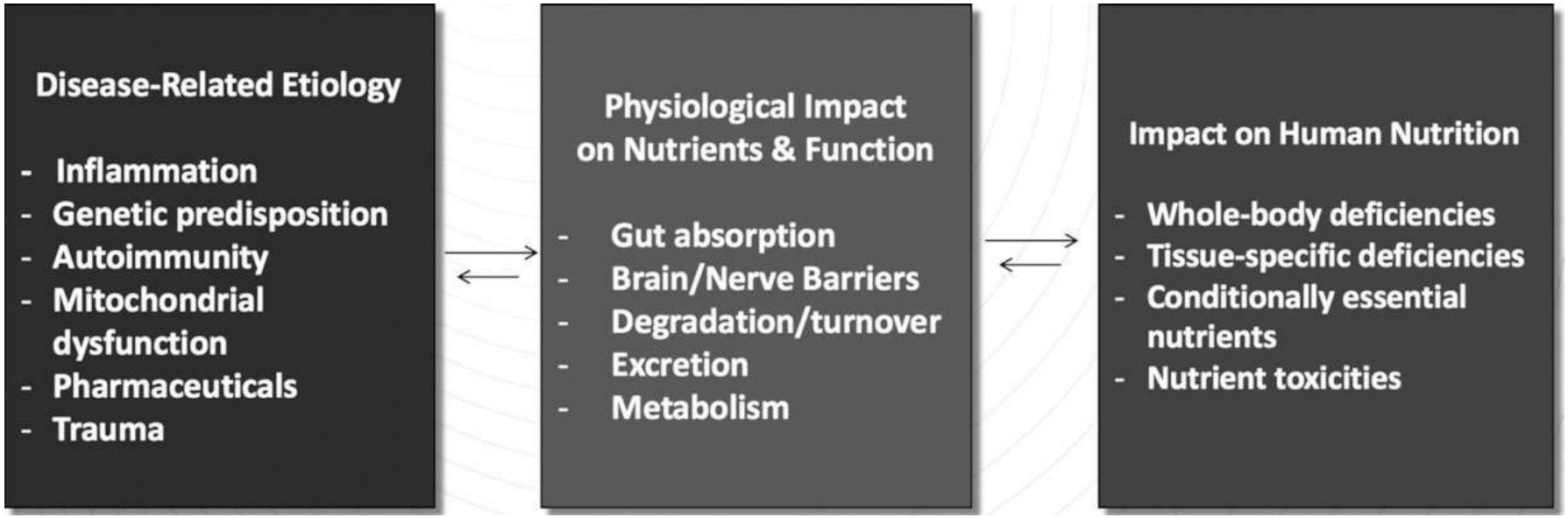
Association Between Social Frailty and Diet in Elderly

Variable	Men				Women			
	GEE β Estimates *	*p* Value	95% CI		GEE β Estimates *	*p* Value	95% CI	
			Lower Limit	Upper Limit			Lower Limit	Upper Limit
a. Factors influencing longitudinal changes based on the dietary diversity score by sex								
Age, years	**0.04**	**0.01**	**0.01**	**0.07**	**0.03**	**0.02**	<0.01	0.06
BMI, kg/m^2	−0.01	0.81	−0.05	0.04	−0.03	0.16	−0.07	0.01
Educational level								
≤9 years	0.00				0.00			
10–12 years	−0.36	0.23	−0.95	0.23	0.11	0.54	−0.25	0.47
>12 years	−0.10	0.73	−0.70	0.49	0.25	0.21	−0.14	0.64
GDS	−0.01	0.70	−0.05	0.04	**−0.03**	**0.04**	−0.07	−0.002
CCI	**0.09**	**0.02**	**0.02**	**0.16**	**0.08**	**0.03**	0.01	0.16
Social frailty status								
Social robustness	**0.00**				0.00			
Social prefrailty and frailty	**−0.25**	**0.01**	**−0.44**	**−0.05**	0.08	0.41	−0.11	0.27

Abbreviations: BMI, body mass index; GDS, Geriatric Depression Scale; CCI, Charlson Comorbidity Index. * GEE β estimates reflect the mean changes in the dependent variable for every 1 year increase in time.

Huang CH et al. Sex-Specific Association between Social Frailty and Diet Quality, Diet Quantity, and Nutrition in Community-Dwelling Elderly. Nutrients. 2020 Sep 17;12(9):2845. doi: 10.3390/nu12092845. PMID: 32957506;

Personalized Patient Nutrition



CLINICAL CONDITIONS THAT AFFECT NUTRITIONAL STATUS AND FUNCTION:

- Chronic inflammation
- Cancer
- Infectious disease
- Trauma and surgery
- Drug-nutrient interactions
- Inborn errors of metabolism
- Loss of barrier function
- Autoimmunity and nutrient transport

New Frontiers of Gender Research

Sex & Gender: the Bias in Nutrition Research

J Acad Nutr Diet. 2023 Feb;123(2):247-252. doi: 10.1016/j.jand.2022.09.014. Epub 2022 Sep 15.

Sex and Gender Data Collection in Nutrition Research: Considerations through an Inclusion, Diversity, Equity, and Access Lens

Heather E Schier, Carolyn Gunther, Matthew J Landry, Sarah D Ohlhorst, Whitney Linsenmeyer

- «**Sex and gender** are often **conflated** in **research, clinical, and administrative settings** in which survey or questionnaire respondents are prompted to select a male or female designation. This practice perpetuates the **erasure of gender minorities** and violates the construct validity of gender as a fluid notion.»

- «**Sex and gender** are **separate health determinants**; conflation of these terms in **data collection undermines** the **precision** and **generalizability** of nutrition research conducted with human subjects»

Q1: What sex were you assigned at birth, on your original birth certificate?

- Female
- Male

(Don't know)
(Prefer not to answer)

Q2: What is your current gender? [Mark only one]

- Female
- Male
- Transgender
- [If respondent is American Indian/Alaska Native (AIAN):] Two-Spirit
- I use a different term: [free text]

(Don't know)
(Prefer not to answer)

The National Academies of Science, Engineering, and Medicine (NASEM) recommended language to query sex and gender.

Beyond Gender

Review > Public Health Nutr. 2021 Dec;24(18):6436-6449. doi: 10.1017/S1368980021001671. Epub 2021 Apr 19.

Expanding the limits of sex: a systematic review concerning food and nutrition in transgender populations

Sávio Marcelino Gomes [1,2], Michelle Cm Jacob [2], Cecília Rocha [3], Maria Fa Medeiros [2], Clélia O Lyra [1], Luiz Ra Noro [1]

Food and nutrition security	Body image and weight control	Nutritional status	Health assistance	Emic views of healthy eating

Final conclusions

Food and nutrition security	Body image and weight control	Nutritional status	Health assistance	Emic views of healthy eating
• Transgender teenagers have a higher consumption of highly processed foods compared to cisgender teenagers. • Transgender teenagers and adults suffer from a high prevalence of food insecurity. • Transgender people have difficulties in accessing food and food programme.	• Transgender people have more body dissatisfaction and eating disorders, varying with the stage of sex change. • Eating disorders, dietary restrictions and weight manipulation strategies for affirming gender are frequent and are related to discriminatory socio-cultural patterns. • Gender reassignment, support networks and security are strategies for relieving symptoms of eating disorders.	• After a year of treatment, there are changes in body fat and muscle mass. • During or after hormonal treatment, transgender people show an increased prevalence of overweight and obesity and increase the consumption of foods high in calories. • Dietary intervention positively impacts transgender people in nutritional counseling about calorie consumption and serum lipid levels.	• The experiences of transgender people in the treatment of eating disorders are marked by stigmatising and discriminatory professional approaches. • We do not know enough about the existence of barriers to nutritional care for transgender peopled. • We need to know more about the role of nutritional care in gender transition.	• The messages on food and nutrition shared on the internet by transgender people are related to diets, exercise and dietary supplements. • We need to know more about the experiences of transgender people with food and its meanings. • We need ethnographic studies to think about food culture, sociability and their associated factors among transgender people.

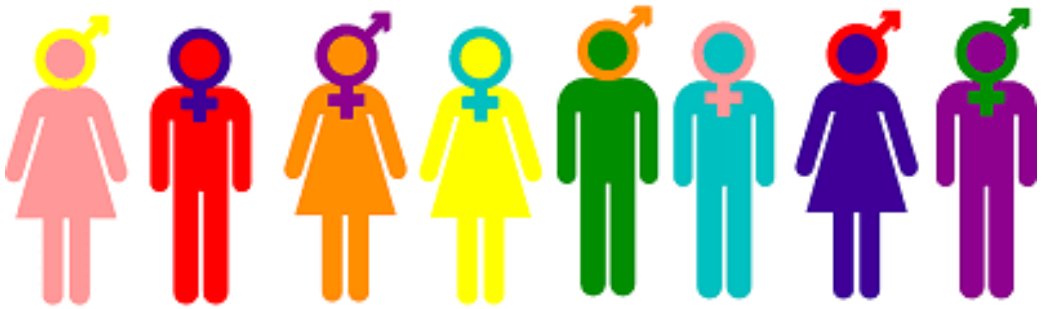
Beyond Gender

› Nutr J. 2020 Jul 16;19(1):74. doi: 10.1186/s12937-020-00590-4.

Towards gender-affirming nutrition assessment: a case series of adult transgender men with distinct nutrition considerations

Whitney Linsenmeyer [1], Theresa Drallmeier [2], Michael Thomure [2]

- **No guidelines** exist for **nutrition assessment** of **transgender** or **gender non-conforming** patients.
- Nutrition assessment methods utilize **gender-specific values** providing **distinct recommendations for males and females**.
- **Further research is needed** to inform nutrition care for the transgender and gender non-conforming populations.



03. Gender Medicine in Surgical Oncology

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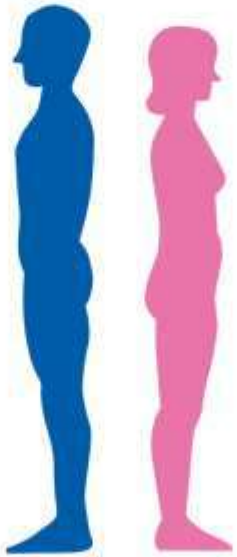
Differences in Cancer Incidence

Estimated New Cases

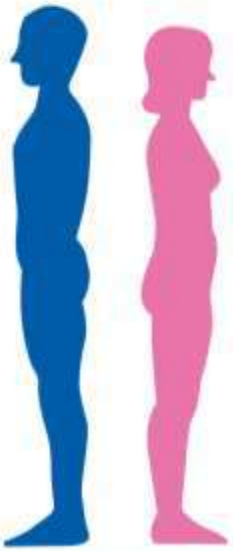
Males				Females		
Prostate	288,300	29%		Breast	297,790	31%
Lung & bronchus	117,550	12%		Lung & bronchus	120,790	13%
Colon & rectum	81,860	8%		Colon & rectum	71,160	8%
Urinary bladder	62,420	6%		Uterine corpus	66,200	7%
Melanoma of the skin	58,120	6%		Melanoma of the skin	39,490	4%
Kidney & renal pelvis	52,360	5%		Non-Hodgkin lymphoma	35,670	4%
Non-Hodgkin lymphoma	44,880	4%		Thyroid	31,180	3%
Oral cavity & pharynx	39,290	4%		Pancreas	30,920	3%
Leukemia	35,670	4%		Kidney & renal pelvis	29,440	3%
Pancreas	33,130	3%		Leukemia	23,940	3%
All Sites	**1,010,310**	**100%**		**All Sites**	**948,000**	**100%**



CA A Cancer J Clinicians, Volume: 73, Issue: 1, Pages: 17-48, First published: 12 January 2023, DOI: (10.3322/caac.21763)

Differences in Cancer Mortality

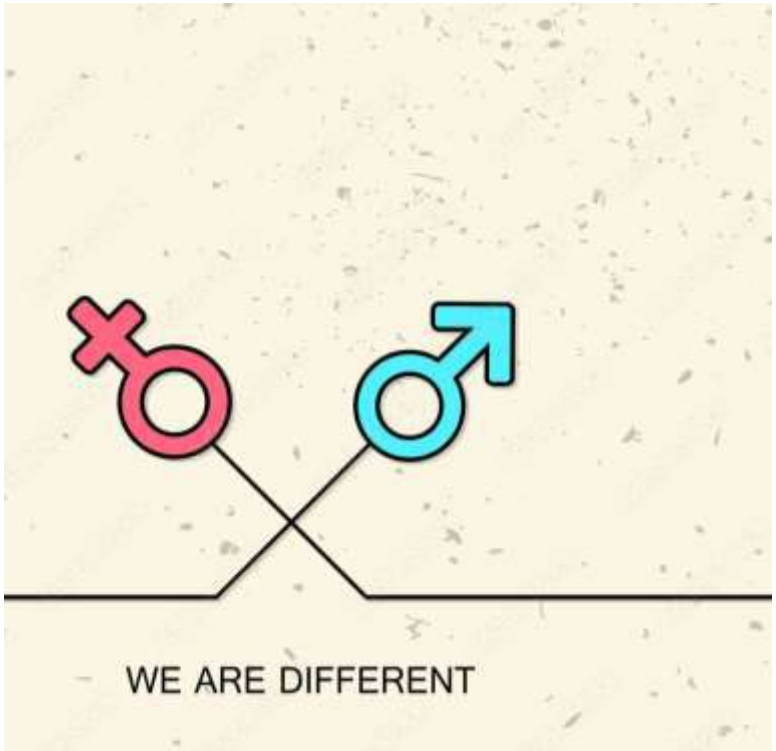
Estimated Deaths

Males				Females		
Lung & bronchus	67,160	21%		Lung & bronchus	59,910	21%
Prostate	34,700	11%		Breast	43,170	15%
Colon & rectum	28,470	9%		Colon & rectum	24,080	8%
Pancreas	26,620	8%		Pancreas	23,930	8%
Liver & intrahepatic bile duct	19,000	6%		Ovary	13,270	5%
Leukemia	13,900	4%		Uterine corpus	13,030	5%
Esophagus	12,920	4%		Liver & intrahepatic bile duct	10,380	4%
Urinary bladder	12,160	4%		Leukemia	9,810	3%
Non-Hodgkin lymphoma	11,780	4%		Non-Hodgkin lymphoma	8,400	3%
Brain & other nervous system	11,020	3%		Brain & other nervous system	7,970	3%
All Sites	**322,080**	**100%**		**All Sites**	**287,740**	**100%**

CA A Cancer J Clinicians, Volume: 73, Issue: 1, Pages: 17-48, First published: 12 January 2023, DOI: (10.3322/caac.21763)

Sex and Cancer Screening Trials

- Women are underrepresented in clinical studies
- In oncological trials women represent bearly 38.8% of the population
- Differences in efficacy of treatment, histology and stage are known but not brought into consideration in daily practice and guidelines



The Italian Journal of Gender-Specific Medicine.
Supplement to Volume 5, Issue 3- 2019

Sex Differences: why do they matter?

- The **balance** between **efficacy and toxicity** may be improved by the development of **rationally designed, sex-specific dose modifications**
- Due to potential **differences** in **tumour biology**, the magnitude of the **treatment benefit** may be **different in men and women**
- Understanding of the **biological basis** of **sex differences** in **tumour biology** might allow for the development of **sex-specific drugs** with greater efficacy

Wagner AD. Sex differences in cancer chemotherapy effects, and why we need to reconsider BSA-based dosing of chemotherapy. ESMO Open 2020;5:e000770. doi:10.1136/esmoopen-2020-000770

04. Gender Differences in Colorectal Cancer

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Differences in CRC Incidence and Mortality

Estimated New Cases

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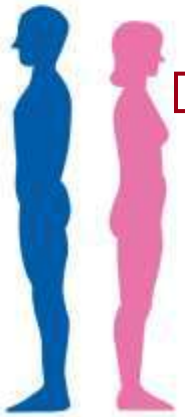

Estimated Deaths

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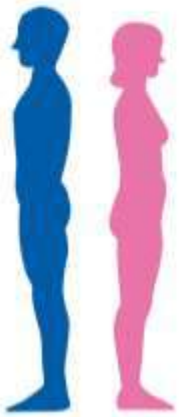


CA A Cancer J Clinicians, Volume: 73, Issue: 1, Pages: 17-48, First published: 12 January 2023, DOI: (10.3322/caac.21763)

Gender Medicine in Surgical Oncology: Colorectal Cancer

- Occurs in women 5 years **later** than in men
- Women are at a **more advanced** stage at diagnosis, and more frequently diagnosed in urgent/emergency situation
- **Survival** of female patients is better

Baggio G, Corsini A, Floreani A, Giannini S, Zagonel V. Gender medicine: a task for the third millennium. Clin Chem Lab Med. 2013 Apr;51(4):713-27. doi: 10.1515/cclm-2012-0849. PMID: 23515103.

Gender Medicine in Surgical Oncology: Colorectal Cancer

- Significant differences in pharmacogenetic basis of **toxicity** of fluoropyrimidines in women; lower toxicity by targeted therapies, such as anti- EGFR drugs in women
- Different impact on **quality of life** for men and women after surgery due to diverse sexual apparatus.

Baggio G, Corsini A, Floreani A, Giannini S, Zagonel V. Gender medicine: a task for the third millennium. Clin Chem Lab Med. 2013 Apr;51(4):713-27. doi: 10.1515/cclm-2012-0849. PMID: 23515103.

Sex- and Gender-specific Disparities in Colorectal Cancer

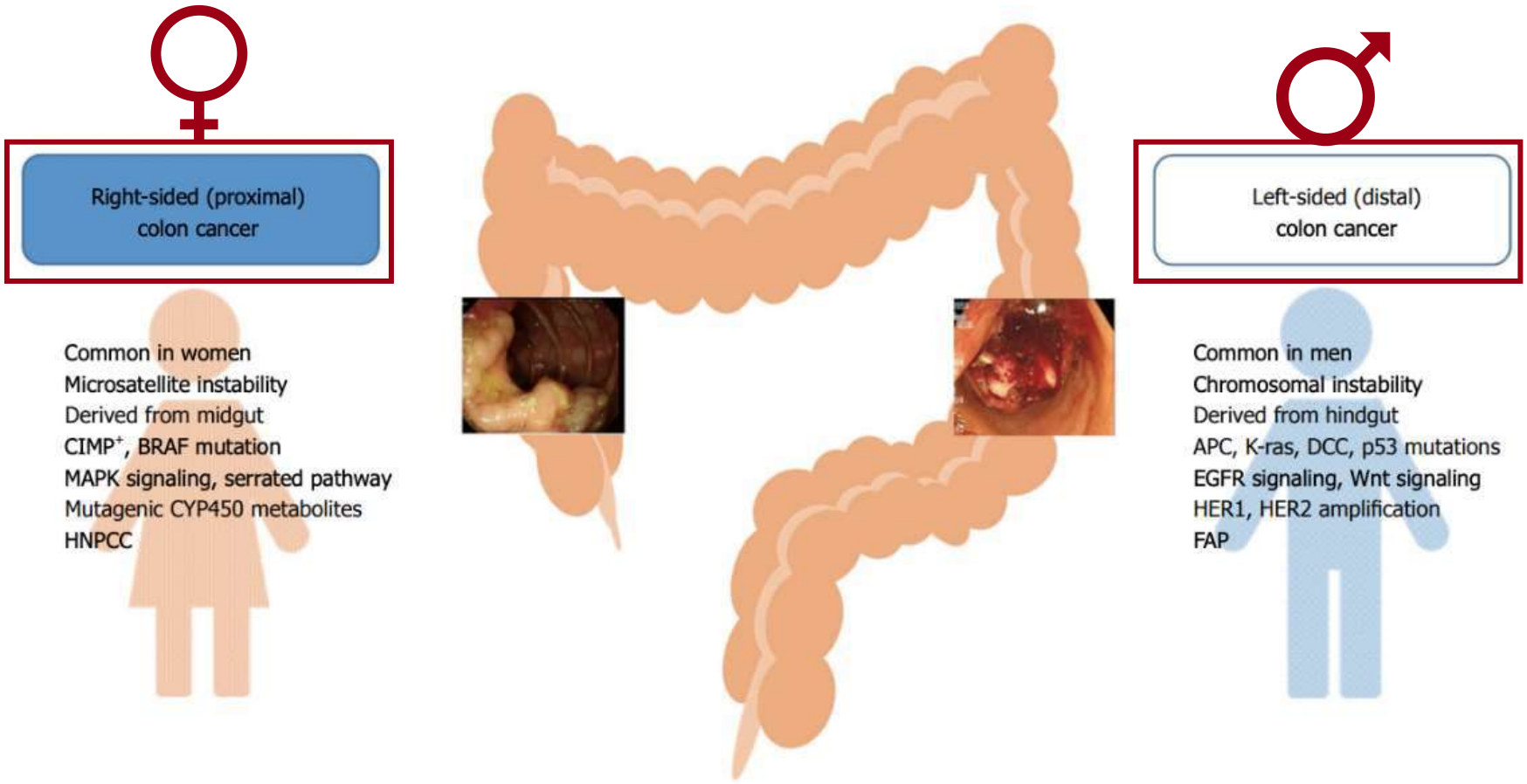


Figure 1 Common clinical and molecular characteristics of right- and left-sided colon tumors. APC: Adenomatous polyposis coli; CIMP: CpG island methylator phenotype; DCC: Deleted in colorectal cancer; FAP: Familial adenomatous polyposis; HNPCC: Hereditary non-polyposis colorectal cancer; K-ras: Kirsten-ras.

Kim SE et Al. Sex- and gender-specific disparities in colorectal cancer risk. World J Gastroenterol. 2015 May 7;21(17):5167-75. doi: 10.3748/wjg.v21.i17.5167. PMID: 25954090; PMCID: PMC4419057.

Screening Efficacy Between Sexes

Faecal Occult Blood Test:

- Detects colorectal tumors at **earlier stage**
- **Reduces mortality** from CRC

BUT

- More **effective** in improving outcomes in **men**

SOLUTION?

- Different cut-offs for men and women

Colorectal Cancer: Post-operative Complications

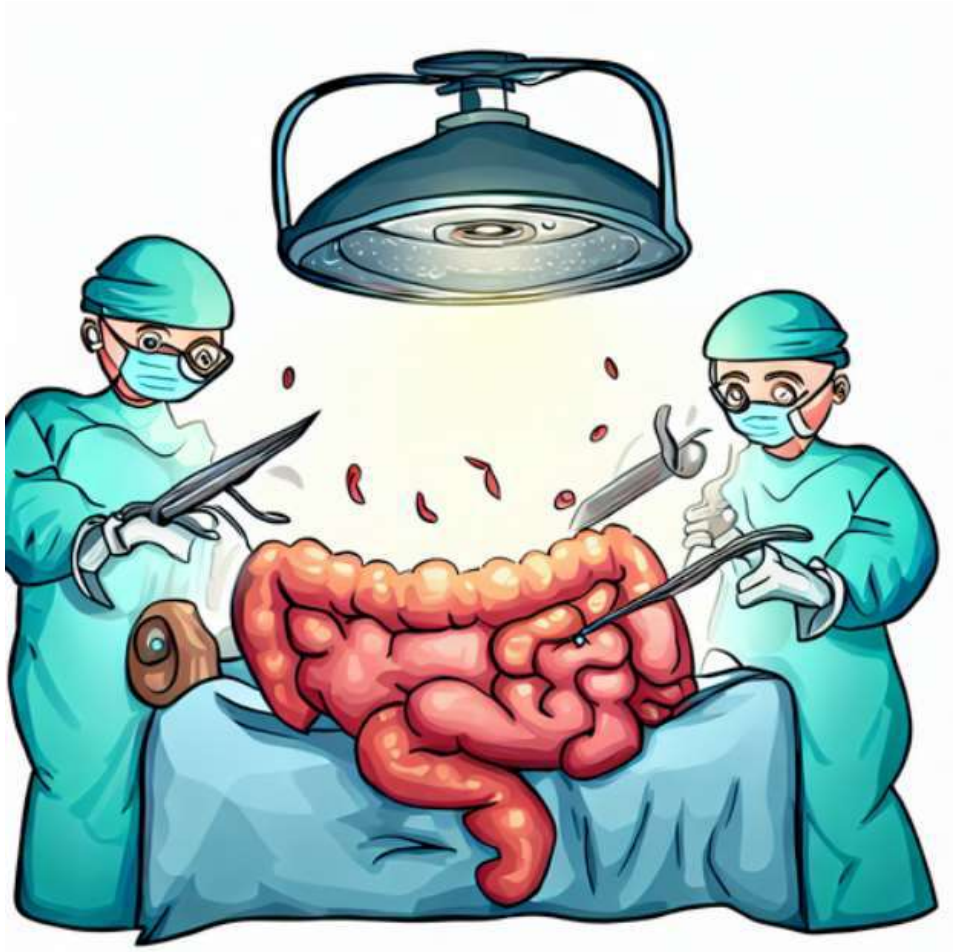
♂

Negative prognostic factors:

- BMI
- ischemic heart disease

Higher rate of:

- surgical site infection
- wound infection
- anastomotic leak in rectal cancer surgery



Colorectal Cancer: Post-operative Complications

Shinji et al. BMC Gastroenterology (2018) 18:117
https://doi.org/10.1186/s12876-018-0846-3

BMC Gastroenterology

RESEARCH ARTICLE Open Access

Male sex and history of ischemic heart disease are major risk factors for anastomotic leakage after laparoscopic anterior resection in patients with rectal cancer

Seiichi Shinji[1*†], Yoshibumi Ueda[2,3*†], Takeshi Yamada[1], Michihiro Koizumi[1], Yasuyuki Masahiro Hotta[1], Takuma Iwai[1], Keisuke Hara[1], Kohki Takeda[1], Mikihiro Okusa[1], Hayato I and Hiroshi Yoshida[1]

JOURNAL ARTICLE

Male gender is associated with an increased risk of anastomotic leak in rectal cancer patients after total mesorectal excision

Chi Zhou, Xian-rui Wu, Xuan-hui Liu, Yu-feng Chen, Jia Ke, Xiao-wen He, Xiao-sheng He, Tuo Hu, Yi-feng Zou, Xiao-bin Zheng ... Show more
Author Notes

Gastroenterology Report, Volume 6, Issue 2, May 2018, Pages 137–143,
https://doi.org/10.1093/gastro/gox039
Published: 14 February 2018 **Article history** ▾

Colorectal Cancer: Survival

WOMEN: ♀

- longer survival in stage I-III
- longer survival in young patients
- more emergent presentation
- older age at presentation
- less aggressive medical treatment

Sex Differences in Quality of Life

Methods and Cohort	Findings	
Disease-free cancer survivors four years after diagnosis N = 1348 	Global HRQoL, physical, role function comparable to the general population, **but emotional and cognitive function worse, especially among women**	
Health-related quality of life (HRQoL) assessed with EORTC QLQ-C30 compared with normative data from general population	**Most frequently reported problems:** - loss of physical performance (36.3%) - fatigue (35.1%) - sexual problems (34.7%) - sleep problems (34.1%) - arthralgia (33.8%) - anxiety (28.0%) - neuropathy (25.6%) - memory problems (23.0%) - concentration problems (21.9%)	Burdened survivors **often rated received support as poor** **Determinants for burden:** higher age female gender having ever received chemotherapy overweight/obesity
Cancer survivors' perceived burdens and **support received for them** was rated for 36 potential symptoms/issues		

➔ A significant number of cancer survivors suffer from long-term or late effects and have unmet care needs.

➔ **Awareness of health care professionals should be increased for these issues.**

➔ Development of targeted survivorship plans.

Late effects, long-term problems and unmet needs of cancer survivors
Martina E. Schmidt,Siri Goldschmidt,Silke Hermann,Karen Steindorf
https://doi.org/10.1002/ijc.34152

05. Take Home Messages

Università degli Studi di Padova

Take Home Messages

Sex disparities have been reported in:

- Genetic
- Epigenetic
- Hormonal
- Clinical and pathological presentation
- Outcomes

Take Home Messages

- **Nutrition** has the **strongest life-long environmental impact** on human **health**.
- **Nutritional studies** can provide clues to understand **pathogenetic** determinants of human **diseases and prevention** strategies
- **Personalized nutrition** and **personalized medicine** are invoked to **adapt food and medicine to individual needs**.
- **Sex-gender differences** are key to obtain **personalized nutrition**
- Despite increasing awareness, **more studies are needed**

Marino M, et al., Nutrition and human health from a sex-gender perspective. Mol Aspects Med. 2011;32(1):1-70. doi:10.1016/j.mam.2011.02.001

Take Home Messages

«In oncology, **sex and gender** as **modulators of disease biology** and **treatment outcomes** are largely unexplored. Considering the increasing evidence **for sex differences in cancer biology and drug effects**, men and women with non-sex-related cancers should **no longer be considered as subgroups**, but as **biologically distinct groups of patients** for whom specific treatment approaches merit consideration.»

Wagner AD, Oertelt-Prigione S, Adjei A, Buclin T, Cristina V, Csajka C, Coukos G, Dafni U, Dotto GP, Ducreux M, Fellay J, Haanen J, Hocquelet A, Klinge I, Lemmens V, Letsch A, Mauer M, Moehler M, Peters S, Özdemir BC. Gender medicine and oncology: report and consensus of an ESMO workshop. Ann Oncol. 2019 Dec 1;30(12):1914-1924. doi: 10.1093/annonc/mdz414. PMID: 31613312.

UNIVERSITÀ DEGLI STUDI DI PADOVA

Thank you

Prof. Gaya Spolverato

Dipartimento di Scienze Chirurgiche Oncologiche e Gastroenterologiche