



Salute e Medicina di Genere

Valeria Raparelli, MD, PhD



Medicina di Genere:
dal piano Nazionale alla clinica,
la salute delle differenze

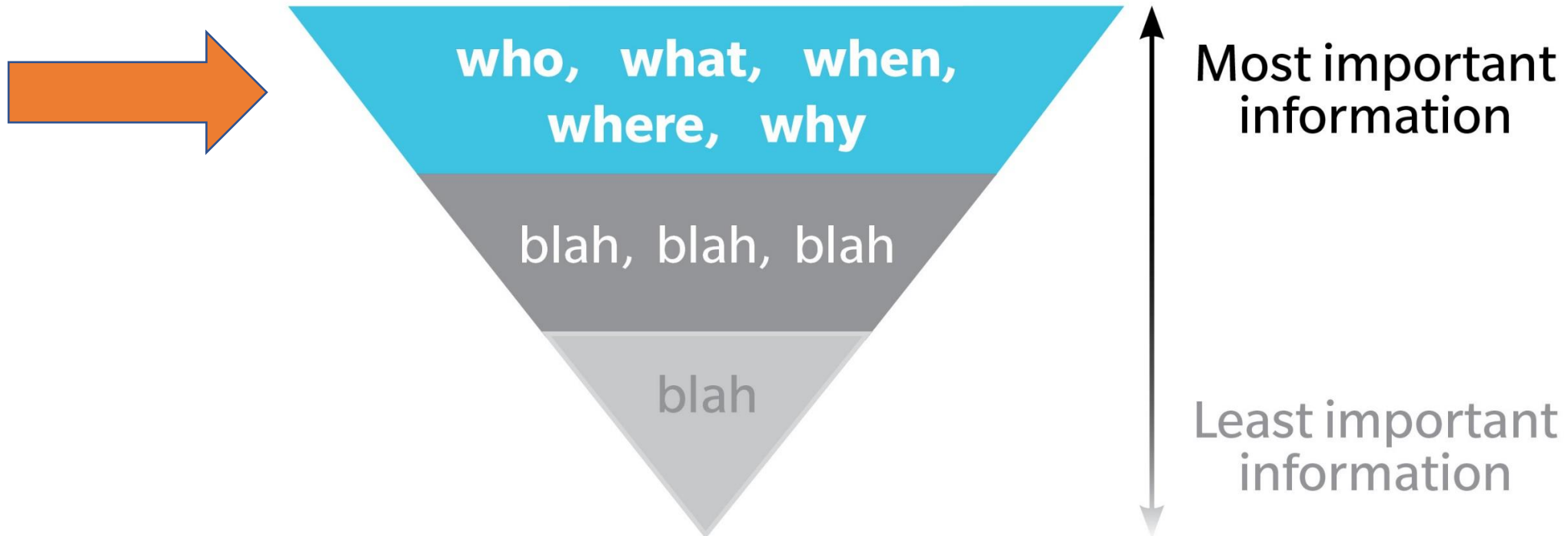


Conflict of Interest Statement: Nothing to disclose

Agenda



Gender and Health: what I have learned





Original Investigation | Public Health

Accuracy in Patient Understanding of Common Medical Phrases

Rachael Gotlieb, MD; Corinne Praska, MD; Marissa A. Hendrickson, MD; Jordan Marmet, MD; Victoria Charpentier, MD; Emily Hause, MD; Katherine A. Allen, MD; Scott Lunos, MS; Michael B. Pitt, MD

Table 4. Statistically Significant Demographic Associations With Correct Understanding of Jargon Phrases on Multivariable Logistic Regression^a

Phrase	Demographic association with correct understanding	Adjusted odds ratio (95% CI)	P value ^b
Your blood culture was negative	Older age (each year) associated with increased understanding	1.03 (1.00-1.06)	.03
The findings on the x-ray were quite impressive	Younger age (each year) associated with increased understanding	0.96 (0.94-0.99)	.002
You are to have nothing by mouth after 4 PM	Older age (each year) associated with increased understanding	1.03 (1.01-1.06)	.002
	Graduate degree associated with increased understanding compared with associate's degree or lower	3.33 (1.39-7.99)	.007
	Bachelor's degree associated with increased understanding compared with associate's degree or lower	2.23 (1.00-4.95)	.049
Your chest x-ray was unremarkable	Graduate degree associated with increased understanding compared with associate's degree or lower	3.45 (1.35-8.87)	.01
You will need to be NPO at 8 AM	Female gender associated with increased understanding	5.65 (1.59-20.13)	.008
Have you been febrile?	Female gender associated with increased understanding	5.90 (1.31-26.71)	.02



"I'll give it to you straight — This disease is almost *impossible* to pronounce."





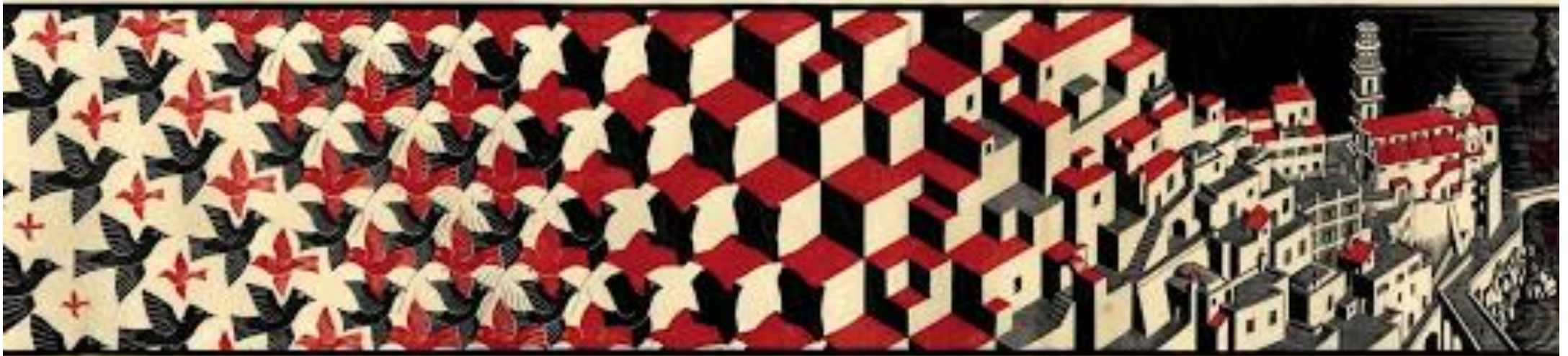
PAST	PRESENT	FUTURE
Intuition Medicine	Evidence-based Medicine	Precision Medicine
Signs and Symptoms	Clinical Trials	Algorithms



***The RIGHT therapeutic strategy
FOR the RIGHT person
AT the RIGHT time***



***Embrace the complexity that a person holds...
when it comes to health***



Escher - Metamorfosi

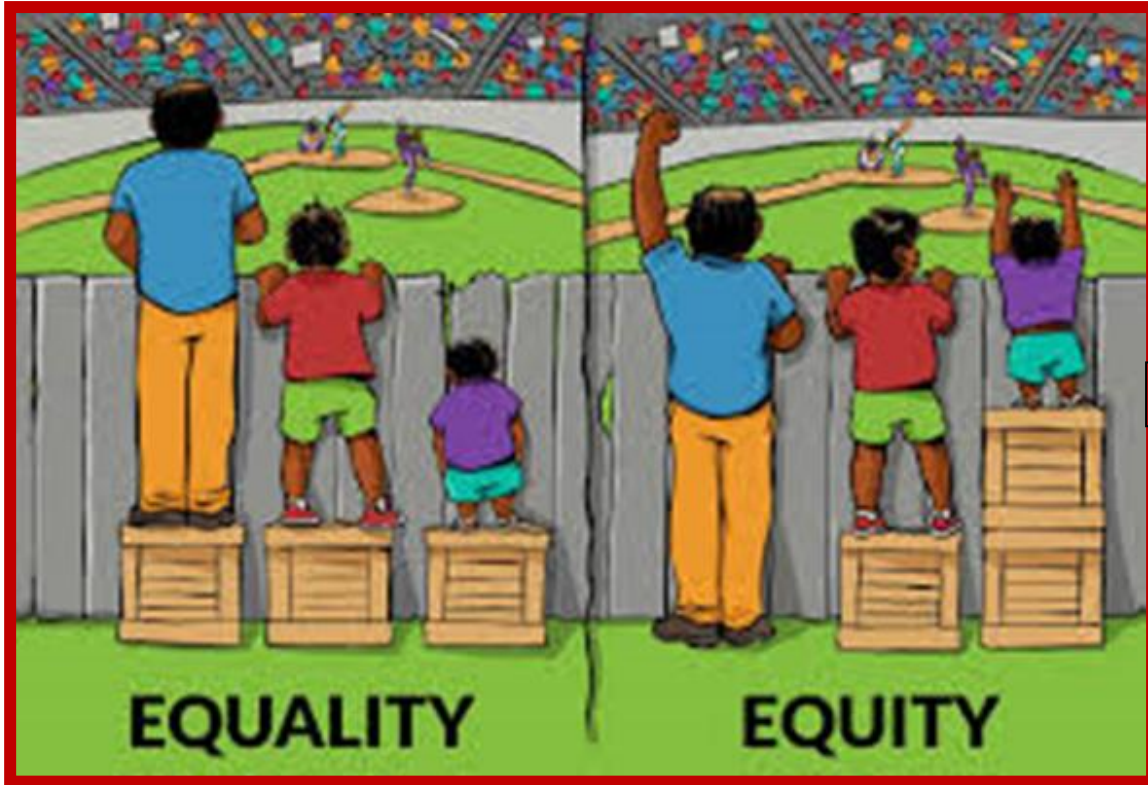


Consider changes over time and across countries

Look over the hedge...



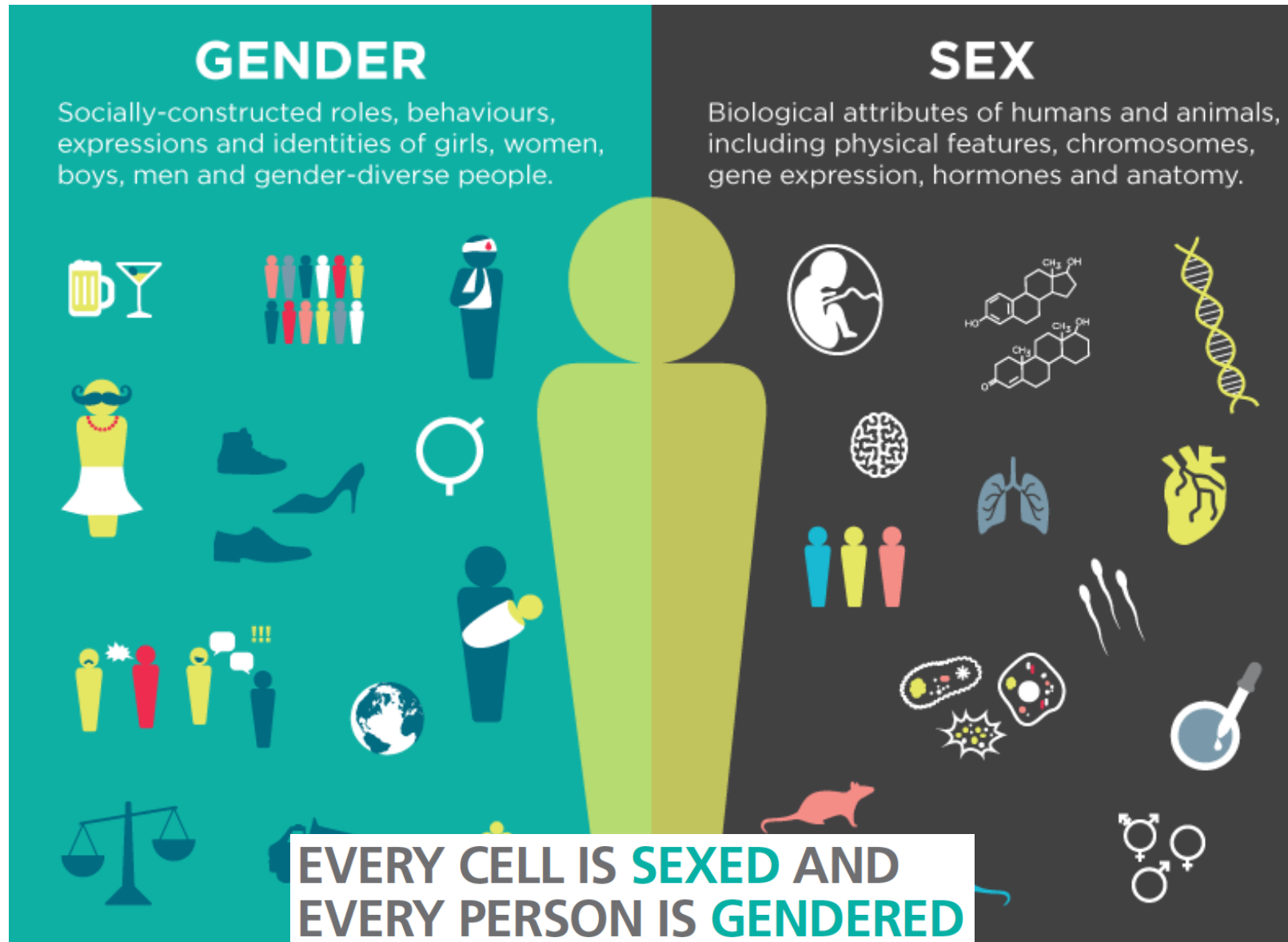
Sex-/Gender- Specific Approach -> Precision Medicine -> Equity



***Multidimensional
Global (holistic)
Approach to Health***

...take into account **INDIVIDUAL VARIABILITY** in genes, environment, and lifestyle for each person... provides strategies that will work in which groups of people

WHAT



SEX AND GENDER ARE NOT SYNONIMOUS



CIHR IRSC

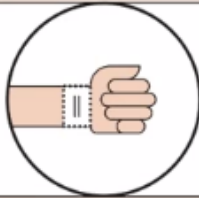
 Canadian Institutes of Health Research Instituts de recherche en santé du Canada

SEX

Sexual characteristics



Assigned sex at birth

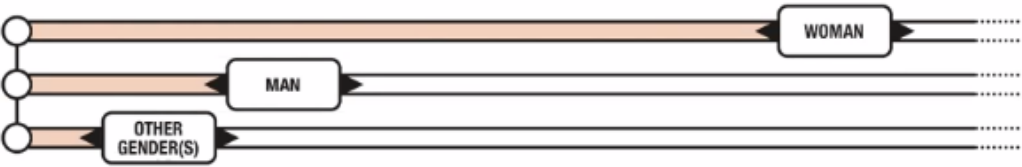


Possibility to modify the legal status

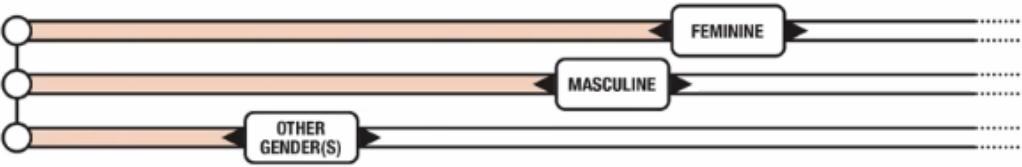


GENDER

Gender identity

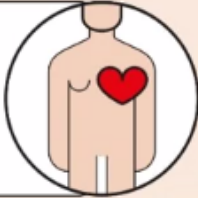
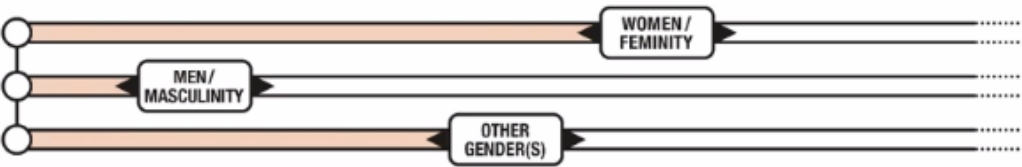


Gender expression

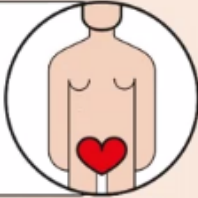
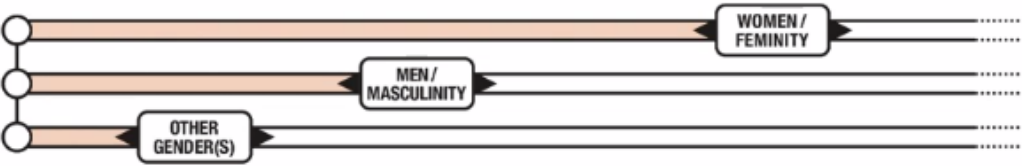


ORIENTATION

Emotional attraction (romantic)



Sexual attraction (erotic)



Note: the way a person defines themselves overrides any other form of categorization.

Bize R, Volkmar E, Berrut S, Werlen M, Medico D, Bodenmann P. (2022)

WHAT is (sociocultural) gender ...

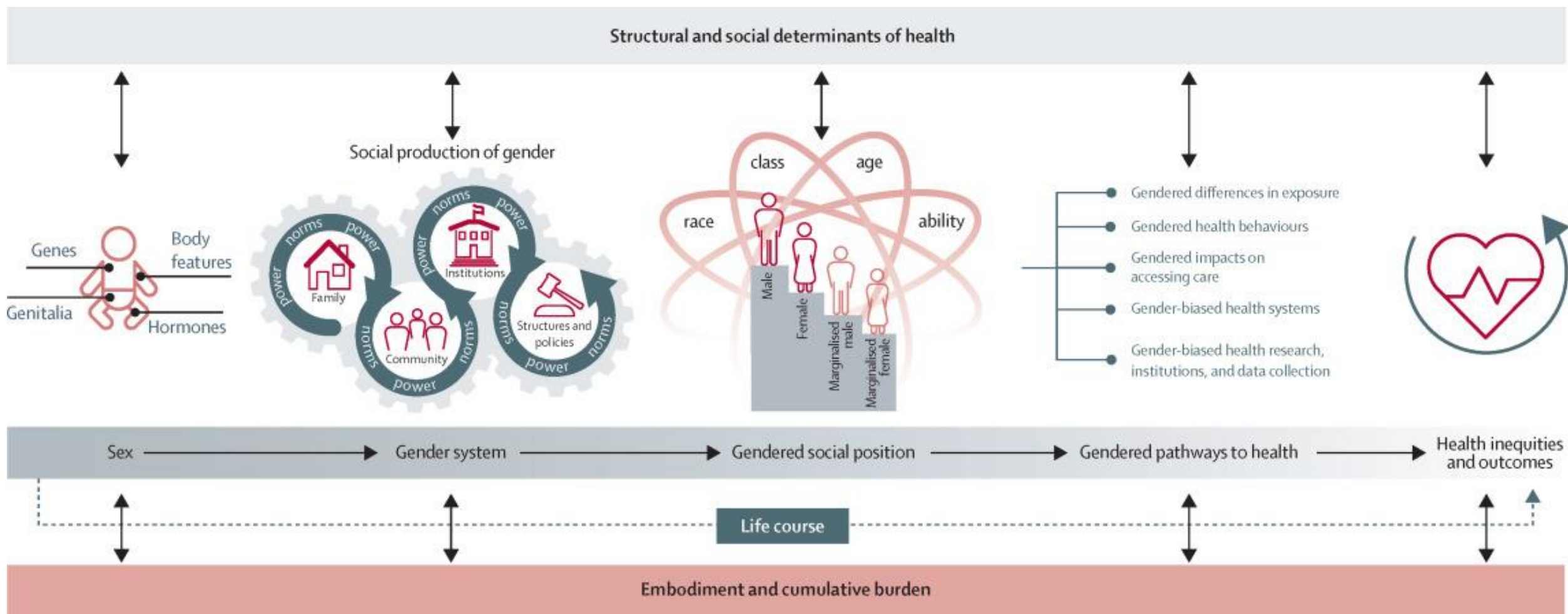


Da dove veniamo? Chi siamo? Dove andiamo? (1897)

Gauguin

WHAT

The intersection of sex and gender



WHY Why gender and diversity in public health interventions?

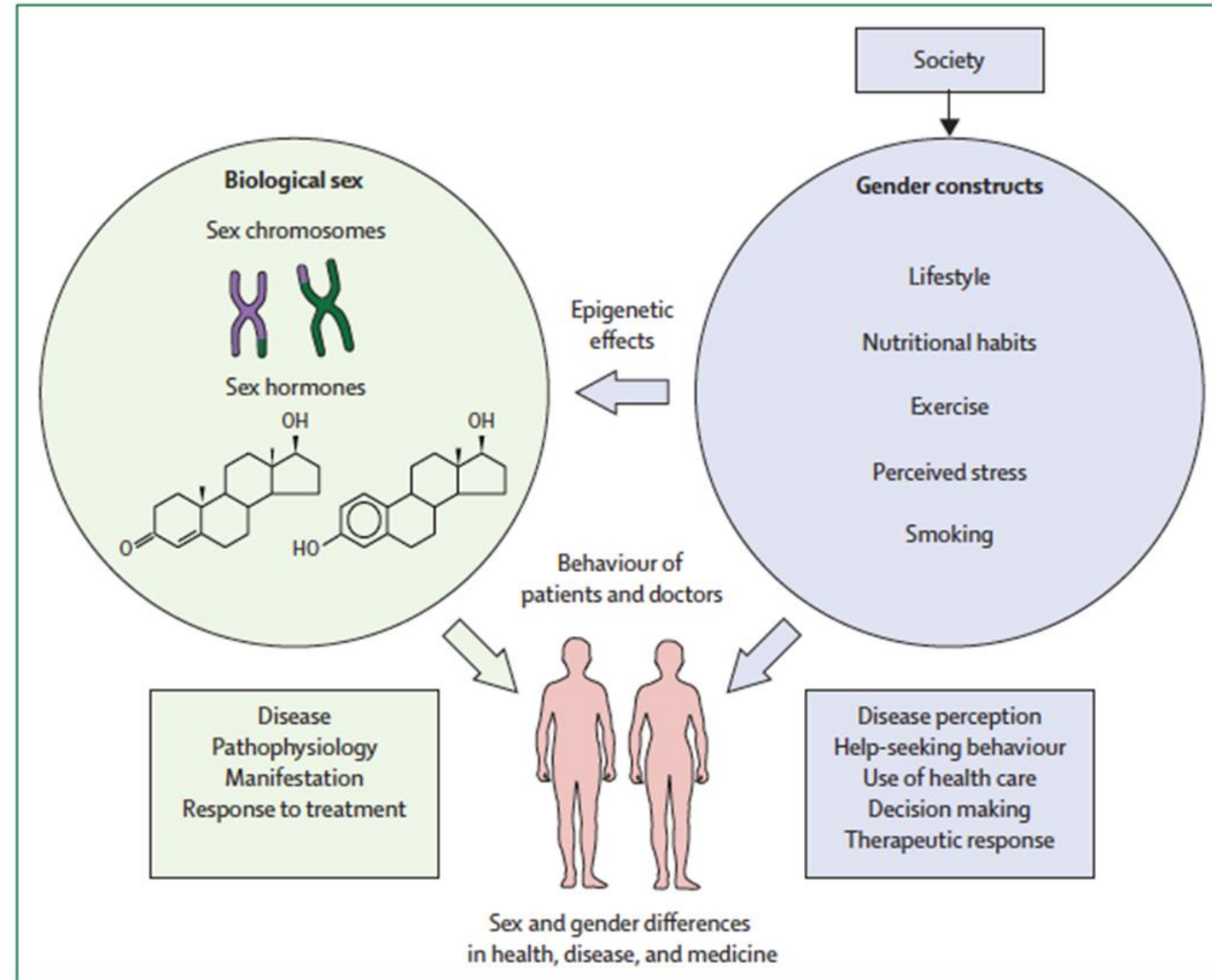


Dimensions	Values/Goals
Ideology	<ul style="list-style-type: none">• (Health) Equity• Remove health inequalities• Social justice• Fight discrimination• Support fundamental rights
Outcomes	<ul style="list-style-type: none">• Health promotion for women and men• Better quality of life
Practice	<ul style="list-style-type: none">• Transdisciplinary teams working on intersectional issues
Empowerment	<ul style="list-style-type: none">• Support informed choice• Offer tools for behavioural change• Acceptance of people's lifestyle choices
Economy	<ul style="list-style-type: none">• Achieve effectiveness• Reduce costs through improvement of measures
Policy	<ul style="list-style-type: none">• Set reasonable goals for health based on differentiated analysis• Maintenance of current state can be a target

WHY Sex and gender: modifiers of health, disease and medicine



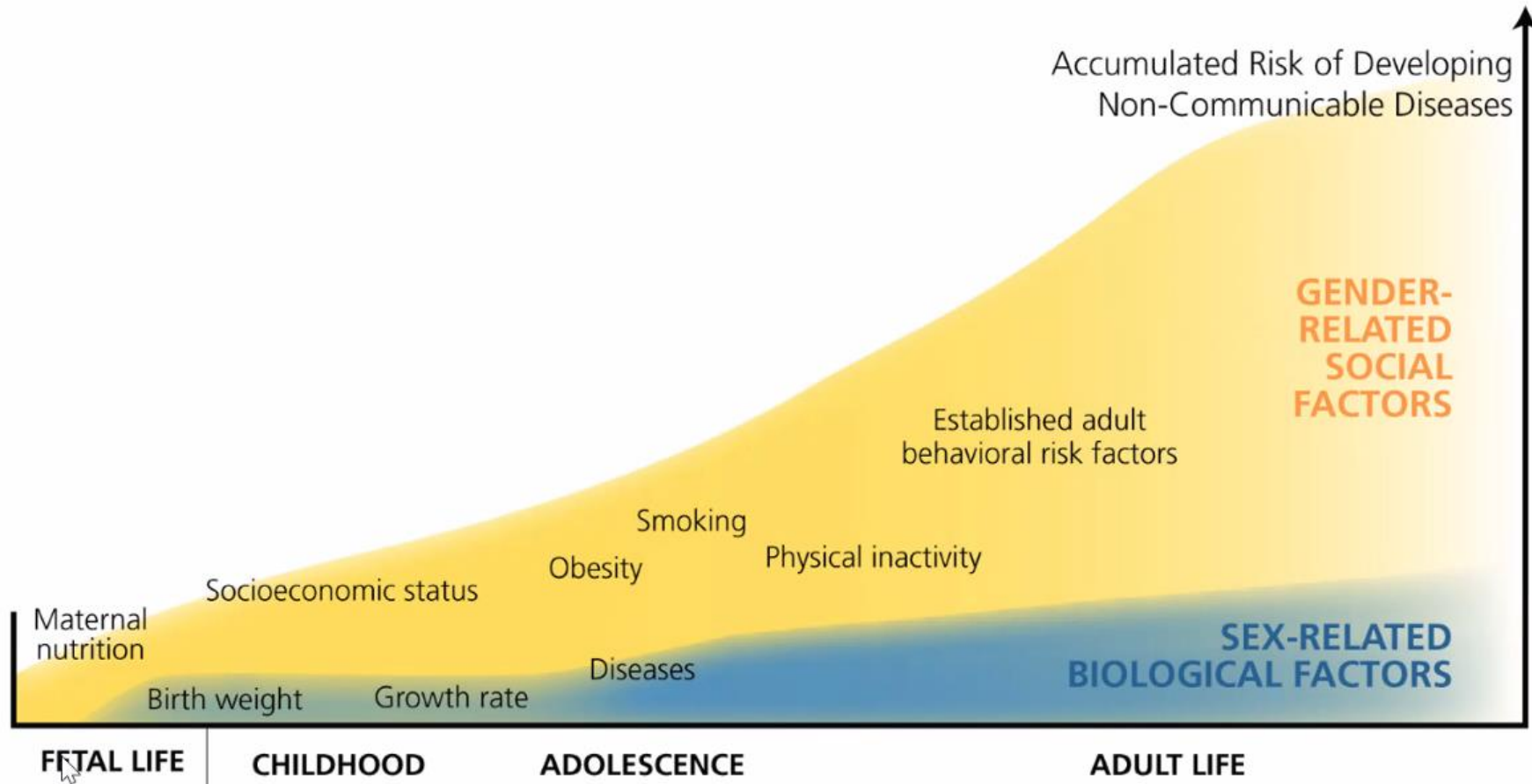
**EQUALLY RELEVANT
FOR HEALTH!**



Gender and the life-course perspective

Cumulative Life Course Risk Factors for Non-Communicable Disease (NCD)

Highlighting the influence of sex and gender-related factors



Adapted from Darton-Hill et al., 2004





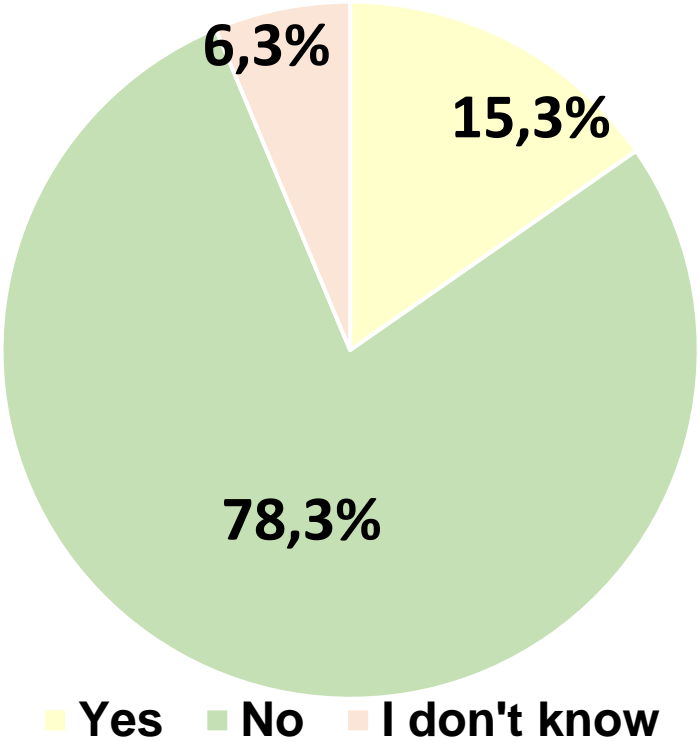
Awareness of sex and gender dimensions among physicians: the European federation of internal medicine assessment of gender differences in Europe (EFIM-IMAGINE) survey

Ewelina Biskup^{1,26} · Alberto M. Marra^{2,27} · Immacolata Ambrosino³ · Elena Barbagelata⁴ · Stefania Basili⁵ · Jacqueline de Graaf⁶ · Asunción Gonzalvez-Gasch⁷ · Risto Kaaja⁸ · Eleni Karlafti⁹ · Dor Lotan¹⁰ · Alexandra Kautzky-Willer^{11,29} · Maria Perticone¹² · Cecilia Politi¹³ · Karin Schenck-Gustafsson¹⁴ · Andreia Vilas-Boas¹⁵ · Jeanine Roeters van Lennep¹⁶ · Emma A. Gans¹⁷ · Vera Regitz-Zagrosek^{18,28} · Louise Pilote¹⁹ · Marco Proietti^{20,21,22} · Valeria Raparelli^{23,24,25} · Internal Medicine Assessment of Gender differences IN Europe (IMAGINE) Working group within the European Federation of Internal Medicine (EFIM)

Received: 26 October 2021 / Accepted: 15 February 2022
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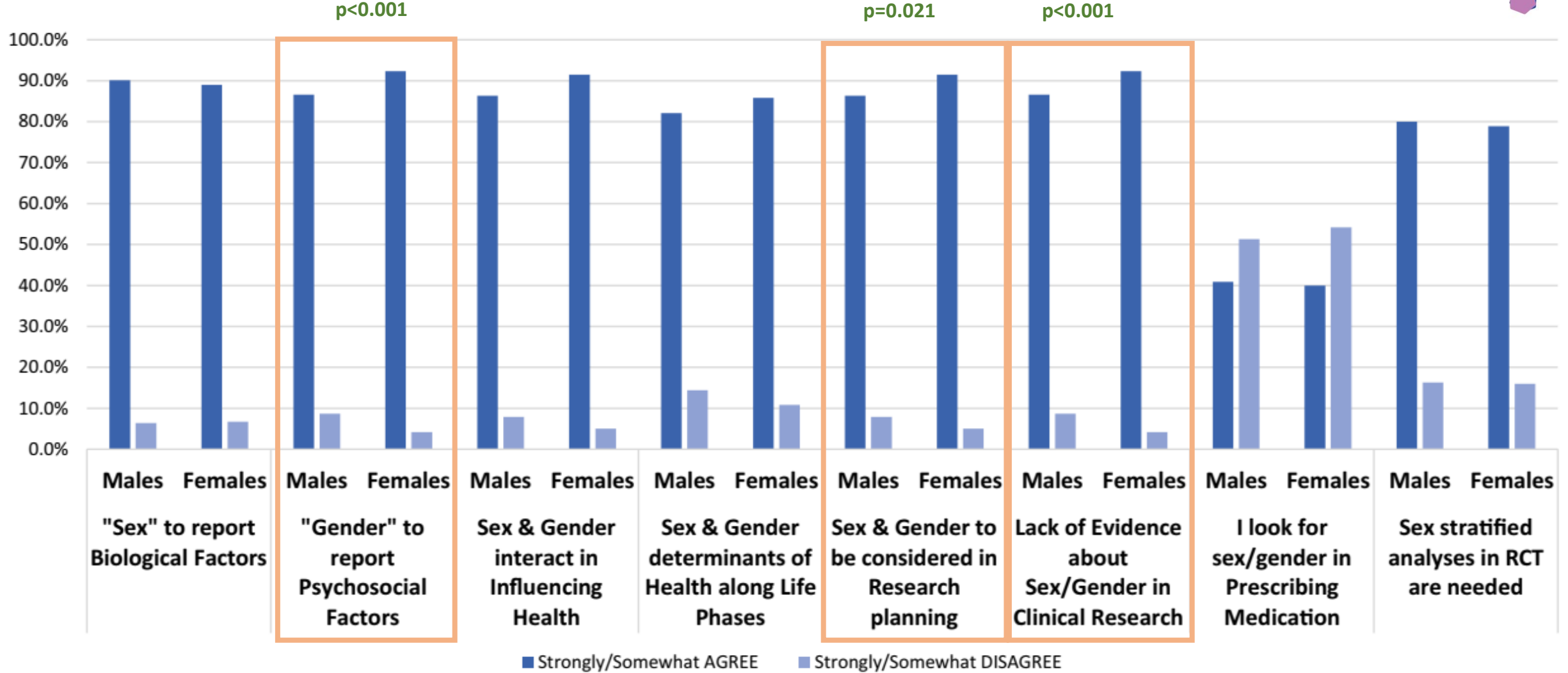
Question 1 - Do you think that the terms "SEX" and "GENDER" are synonymous?



Please for the following variables select the most appropriate condition (tick the ones you think are sex-related, gender-related or both or not?) *

	Sex Related	Gender Related	No sex and gender related	I don't know
Age	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Genetics	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Sex Hormones	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Reproductive status	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Marital Status	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Ethnicity	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Personality Traits	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Body Composition	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Religion	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Diet	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Smoking Habit	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Alcohol	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Sexual Orientation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Environment	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Working Status	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Body size	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Geographic Location	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Disability	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Co-Morbidities	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Socioeconomic Status	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

	Sex Related	Gender Related	Sex & Gender Related	No Sex & Gender Related	Don't Know
Body Size	49.9%	15.0%	14.6%	17.9%	2.6%
Genetics	66.4%	11.5%	12.8%	6.0%	3.4%
Sex Hormones	66.1%	11.7%	18.7%	1.5%	1.9%
Reproductive Status	64.0%	12.9%	16.9%	3.5%	2.7%
Body Composition	54.0%	18.8%	20.2%	4.8%	2.2%
Diet	8.3%	32.9%	14.2%	40.1%	4.5%
Marital Status	10.6%	41.6%	12.9%	27.6%	7.3%
Personality Traits	6.8%	44.7%	21.1%	20.6%	6.8%
Socio-Economic Status	6.9%	35.4%	17.6%	35.4%	4.7%
Working Status	8.9%	38.8%	17.2%	31.6%	3.6%
Alcohol	9.9%	34.8%	12.2%	39.6%	3.4%
Smoking Habit	8.0%	34.0%	11.3%	42.2%	4.5%
Ethnicity/Race	8.2%	20.6%	5.1%	59.9%	6.2%
Religion	2.2%	22.3%	4.2%	64.9%	6.4%
Age	22.4%	10.4%	8.2%	54.9%	4.2%
Comorbidities	33.1%	18.9%	21.8%	22.1%	4.1%
Disability	7.1%	13.5%	6.3%	63.7%	9.3%
Geographic Location	4.1%	16.0%	3.9%	66.6%	9.4%
Environment	4.3%	30.7%	8.8%	45.7%	10.5%

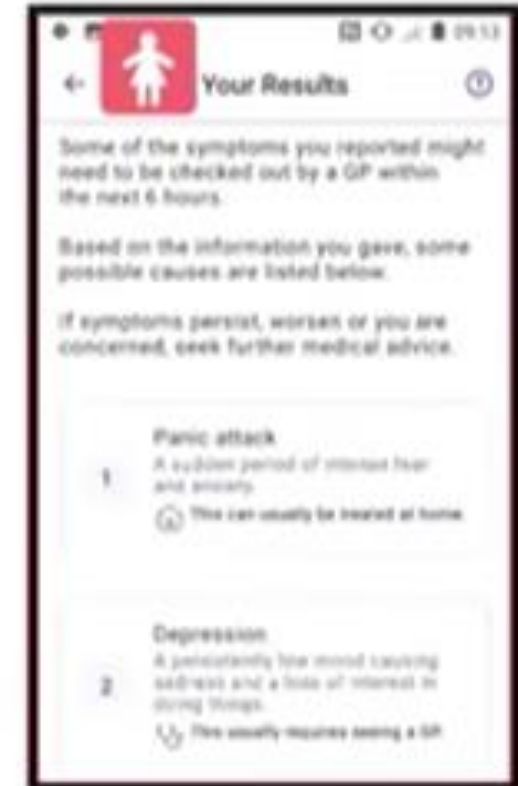


PANEL B

WHY – Do not harm!



56 yrs, smoker, left arm pain associated with sweating lasting more than 1 hour...



#deathbychatbot



HOW CAN I ACCOUNT FOR GENDER IN CLINICAL RESEARCH?

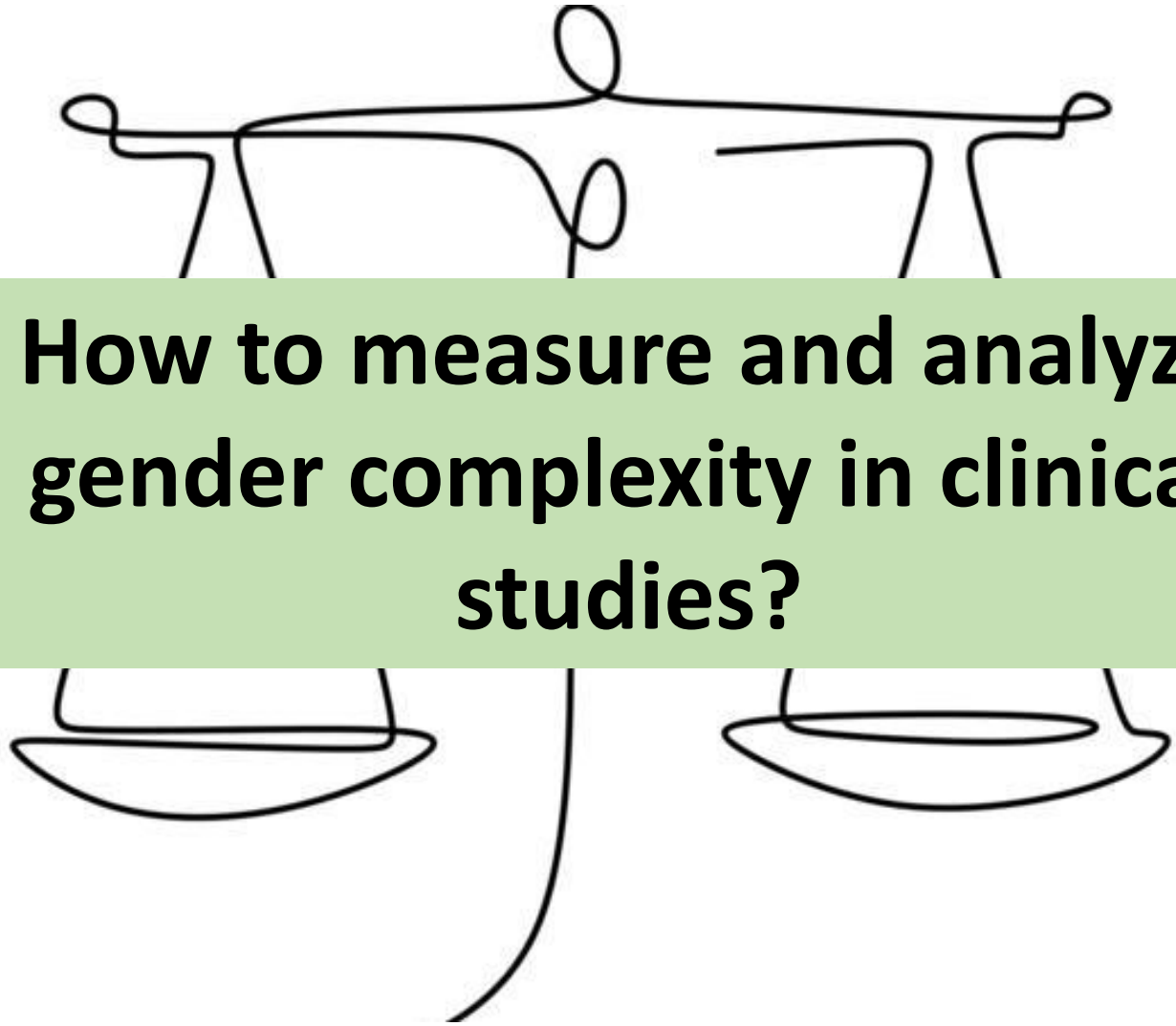
Data Collection – the first obstacle



1. ARE GENDER-RELATED VARIABLES
COLLECTED IN CLINICAL STUDIES?

- ✓ **MAINLY NO!**
- ✓ **YET WE CAN IMPROVE...How?**



A simple line drawing of a balance scale, centered behind the text. It features a horizontal beam supported by two vertical stands, with two pans hanging from the ends. The scale is currently balanced.

How to measure and analyze gender complexity in clinical studies?

The GOING-FWD Team: Diversity, Gender Expertise and Gender Equality Measures

Co-Principal Investigators

Louise Pilote



Colleen Norris



Valeria Raparelli



Monica Parry



Site Principal Investigators

Alexandra Kautzky-Willer



Karolina Kublickiene



Maria Trinidad Herrero



Co-Investigators

Canada

Karin Humphries

Ruth Sapir-Pichhadze

Michal Abrahamowicz

Khaled El Emam

Simon Bacon

Austria

Peter Klimek



GENDER-NET Plus
Promoting gender equality in H2020 and the ERA

Early Career Investigators (8)

Canada:

Z. Azizi, R. Dev, C. Tadiri

Austria:

S. Linder, T. Gisinger, J. Harreiter

Sweden:

L. Ward

Spain:

A.M. Lucas

Other trainees (15)

Canada (3)

Austria (2)

Rome (3)

Sweden (2)

Spain (5)

Scientific Advisory Committee

Vera Regitz-Zagrosek

Londa Schiebinger

Carole Claire

Rachel Dryer

Patient Partners (7)

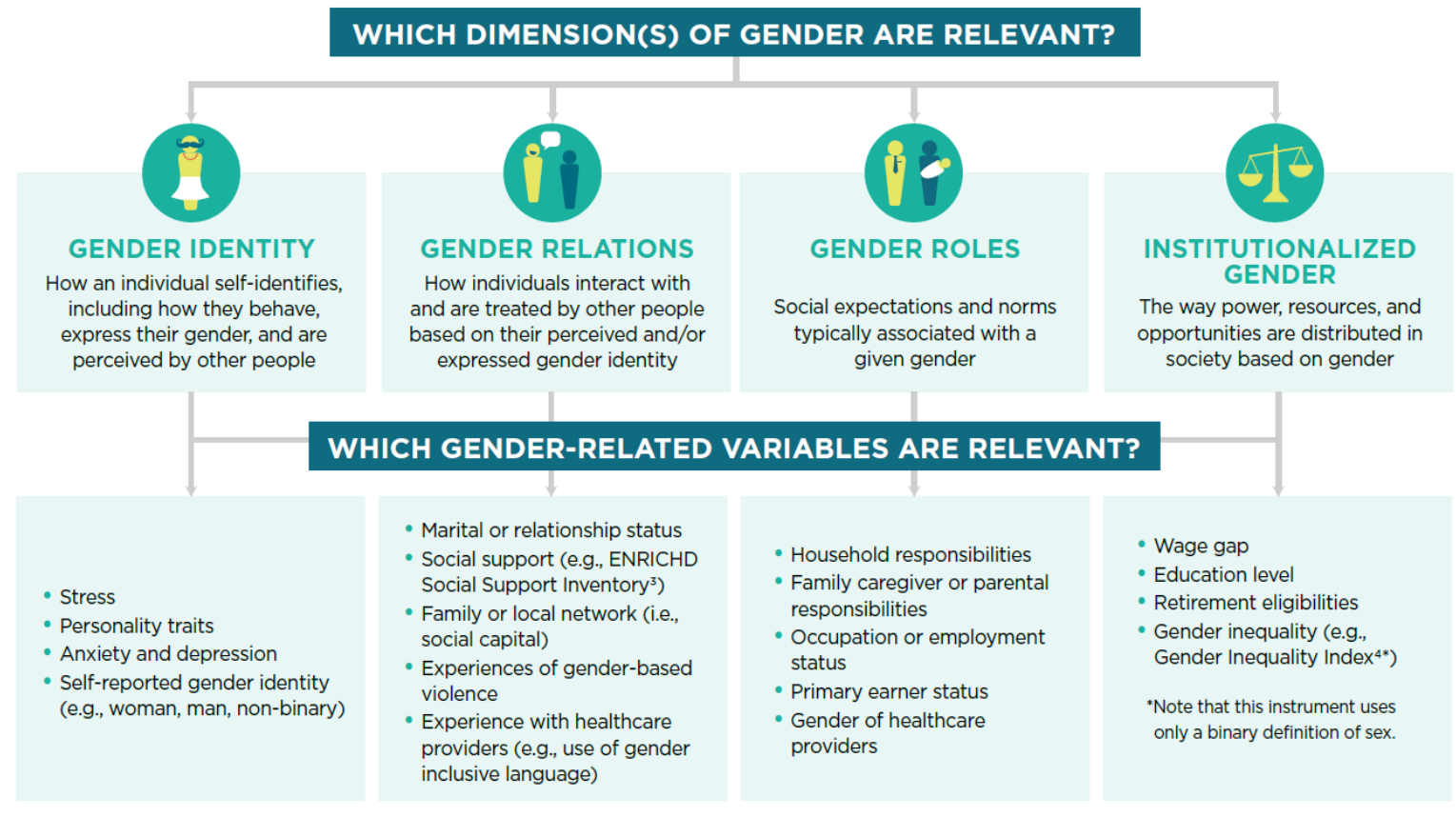
GENDER = MULTIDIMENSIONAL PSYCHO-SOCIO-CULTURAL CONCEPT



What is a gender-related variable?

A gender-related variable is a **non-biological variable** which differs in terms of magnitude, prevalence, and/or impact between people of different genders (men, women, gender-diverse people).

Gender can be broken down into 4 dimensions

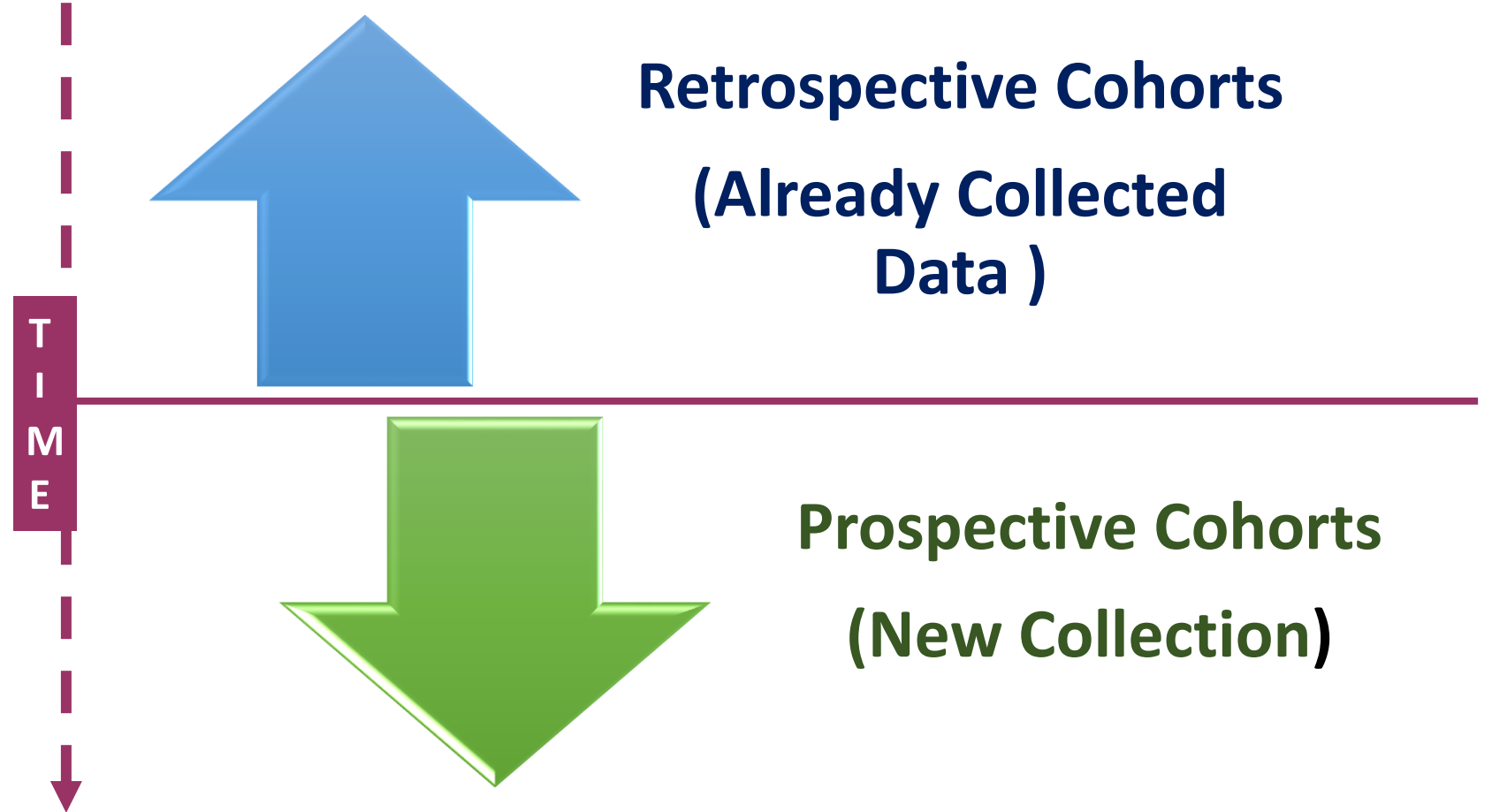


Pilote L, Norris CM and Raparelli V. Methods for Prospectively and Retrospectively Incorporating Gender-Related Variables in Clinical Research - <https://cihr-irsc.gc.ca/e/52608.html>

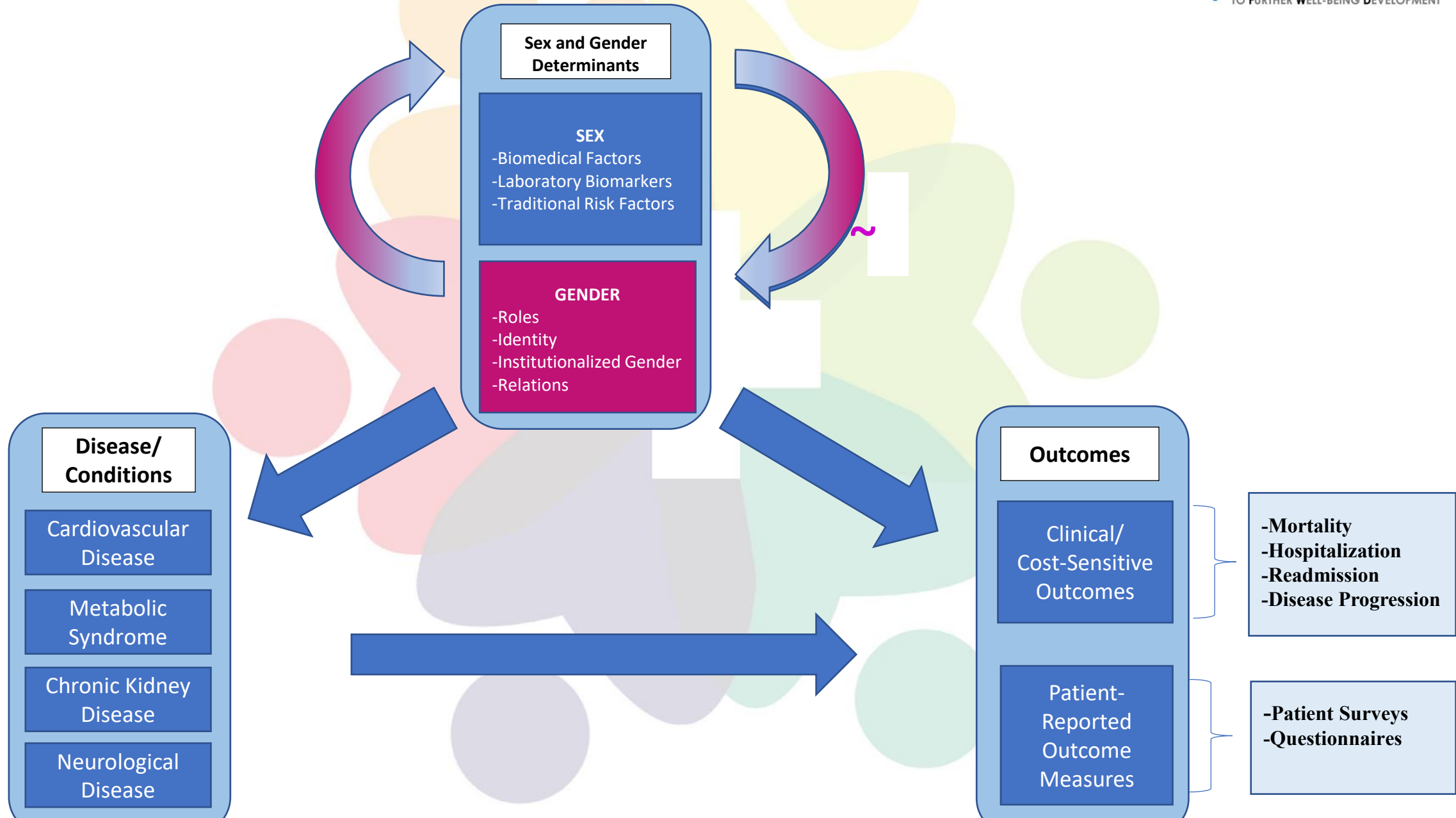
WHEN AND WHERE

Clinical Scientists – which data to use for answering a research question

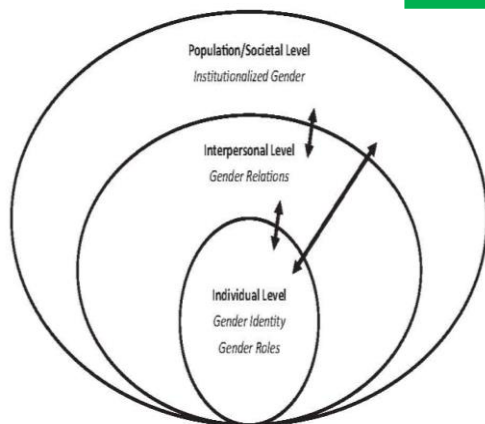
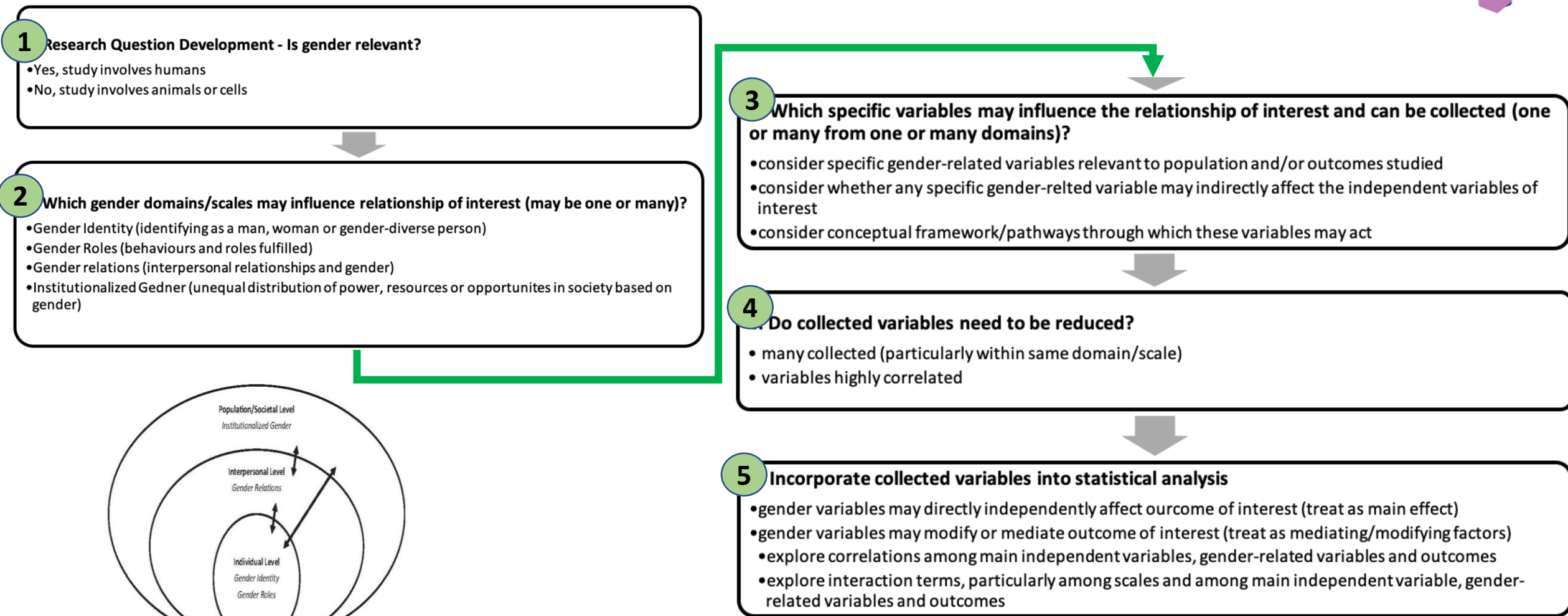
2 Scenarios

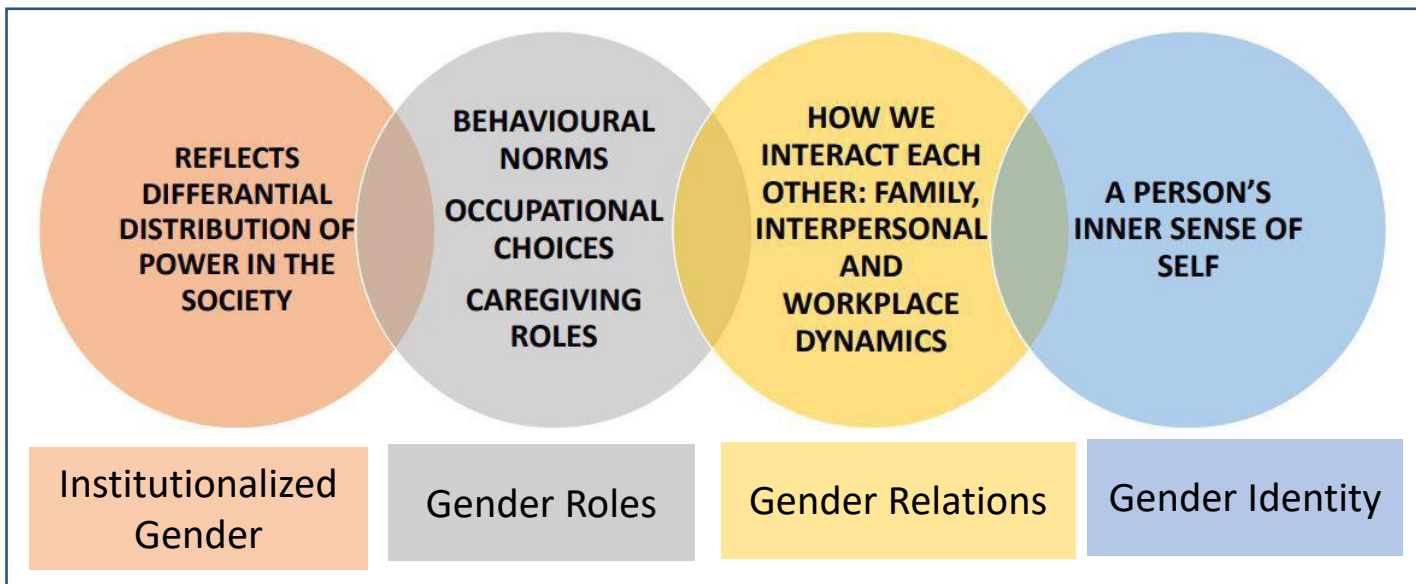


Conceptual framework



Gender Measurement (Prospective)





Practice

BMJ Global Health

Identification and inclusion of gender factors in retrospective cohort studies: the GOING-FWD framework

Valeria Raparelli,^{1,2} Colleen M. Norris,² Uri Bender,³ Maria Trinidad Herrero,⁴ Alexandra Kautzky-Willer,⁵ Karolina Kublickiene,^{6,7} Khaled El Emam,^{8,9,10} Louise Pilote,^{3,11} GOING-FWD Collaborators

STEP 1 -
**IDENTIFICATION OF
GENDER-RELATED
VARIABLES**

STEP 2 -
**DEFINITION OF
OUTCOMES**

STEP 3 -
**BUILDING OF
FEASIBLE FINAL
VARIABLES LIST**

STEP 4 -
**RETROSPECTIVE
DATA
HARMONIZATION**

STEP 5 -
**DEFINITION OF
DATA
STRUCTURE**

Developing a Methodology for Data Harmonization



Data Harmonization

Cohorts

- GENESIS PRAXY
- APPROACH
- EVA
- VIRGO
- ALBERTA HEALTH SERVICES
- REWARD
- DECADE
- MOSMI
- CPCSSN
- MAIN ASSOCIATION OF AUSTRIAN SOCIAL SECURITY INSTITUTIONS
- AT-HIS
- E-HIS
- IMPROVED
- HEALTH MURCIA SERVICE (SMS)
- HEALTH RIOJA SERVICE (HRS)
- DAC
- DAC2
- DALI
- MIA
- NJURBIOPSIPROJEKTET
- KOPIA
- HEARTIS
- MBDS
- OEDTR
- MS DATASET
- CCHS
- BIOBANK
- STEPS

Variables

Demographics

Age
Date of Birth (DOB)
Sex
Ethnicity
Language
Country of residence
Country of Origin
Province/Region
Ethnic background of parents
Rural/Urban Status
Country of Birth/ Birth place
Current living situation (with partner, parents, etc.)
Postal code
Address

Gender Roles

Primary earner status
Employment Status
Occupation
Work hours per week
Level of responsibility for disciplining children
Number of hours per week spent on housework
Status of household's primary responsibility
Number of children
Social status

Gender Relations

Marital/Relationship Status
Social support
ENRICH social support instrument
Availability of Caregiver
Medical Outcomes Study (MOS)
Social Support Survey

Institutionalized gender

Educational Level
Number of years of schooling
SES/Income
Monthly finances
Household income
Investments (stocks, bonds etc.)
Perceived Social Standing
GII (Gender inequality index)
Type of maternity care

Gender Identity

Stress
14-Item Perceived stress scale (PSS)
Stress level at work
Stress level at home
Stress management
Wellness

Personality traits

Emotional intelligence
BEMS (instrument)
Marlowe-crowne question (assesses personality, temperament, and demeanor)

Depression/Anxiety

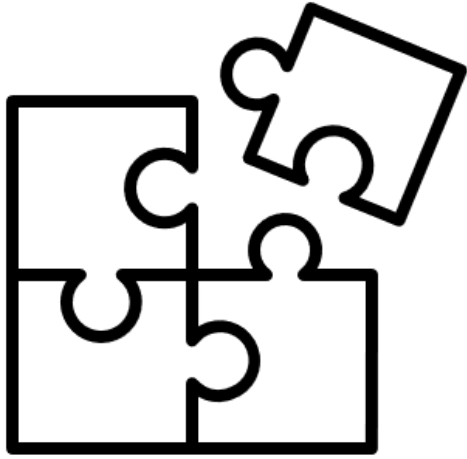
Patient Health Questionnaire-9
HAD Scale - Hospital Anxiety and Depression Scale
Anxiety/Depression
Anxiety sensitivity question
Beck depression inventory question
Pill question (?)
Tas questions (?)
State-Trait Anxiety Inventory (STAI) (quantifies adult anxiety)
Beck anxiety inventory question

Other psychiatric questionnaires

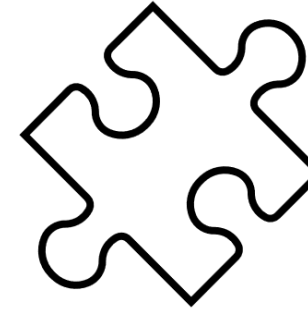
Whiteley index questions (assesses hypochondria)
Discrimination
Day-to-day experiences

HOW.... CAN I ACCOUNT FOR GENDER IN MY ANALYSIS PLAN?

Clinical Scientists – Options on how to deal with data



COMPOSITE
MEASURE OF GENDER



INDIVIDUAL
GENDER-RELATED FACTORS

*It depends on the richness of your
database and on the research question!*

SEX AND GENDER IN PRECISION MEDICINE

Beyond sex, gender predicts better clinical outcomes



GENDER SCORE



1. Primary household earner status
2. Personal income
3. Number of hours per week doing housework
4. Primary responsibility for doing housework
5. Level of stress at home
6. Bem Sex Role Inventory masculinity score
7. Bem Sex Role Inventory femininity score

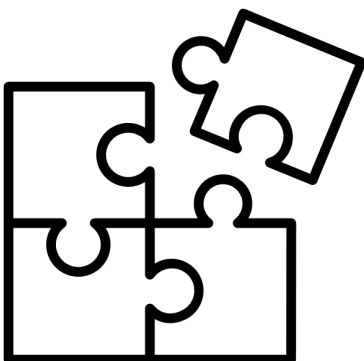
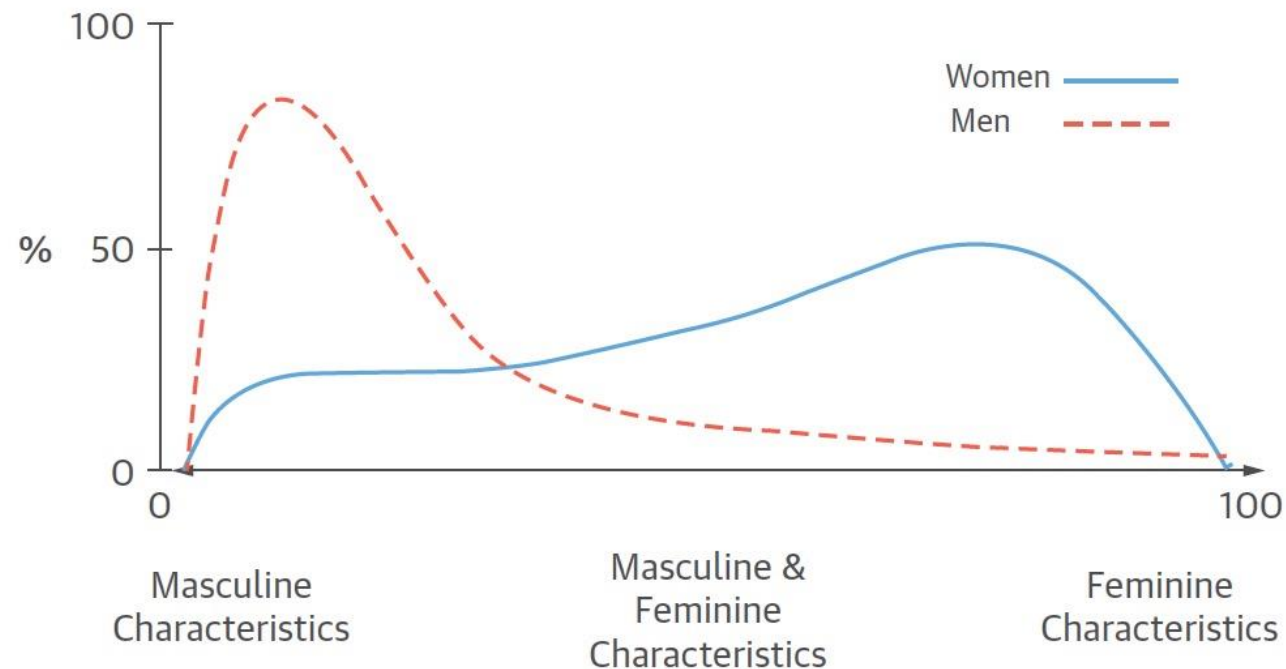
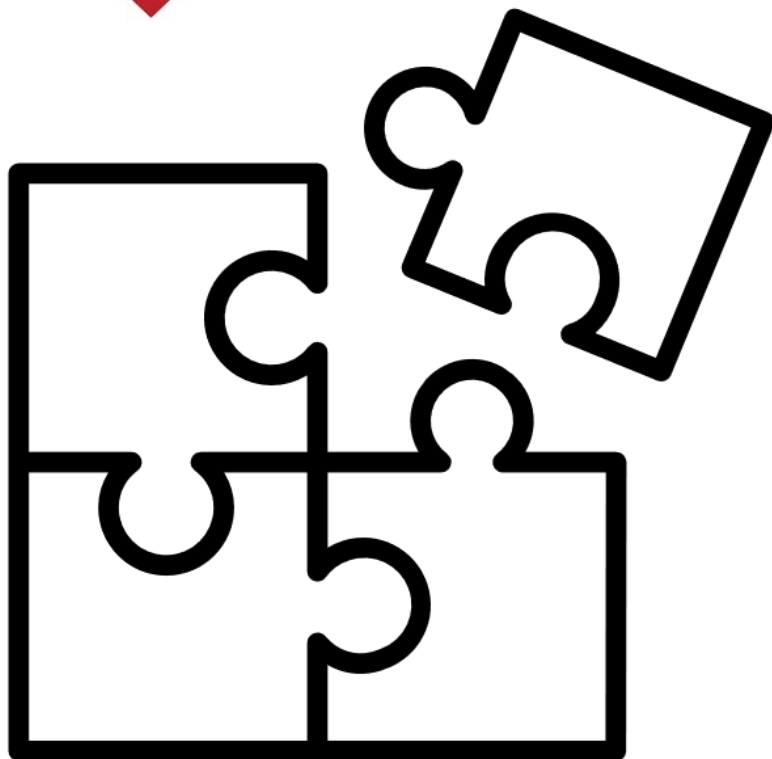


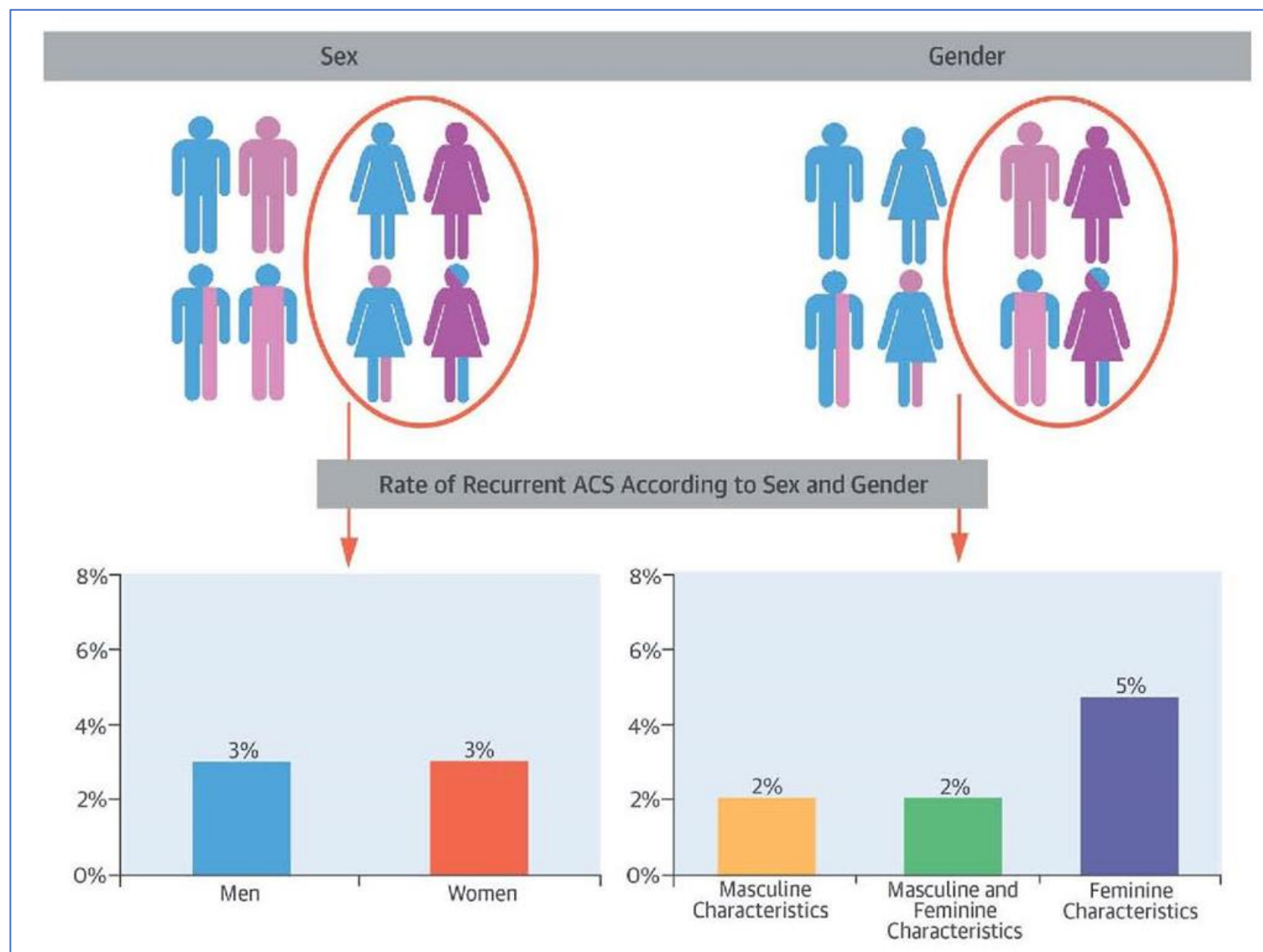
FIGURE 1 Gender Score Distribution in Men and Women With Premature Acute Coronary Syndrome





Adapted with permission from Pelletier et al. (22).



Gender Score



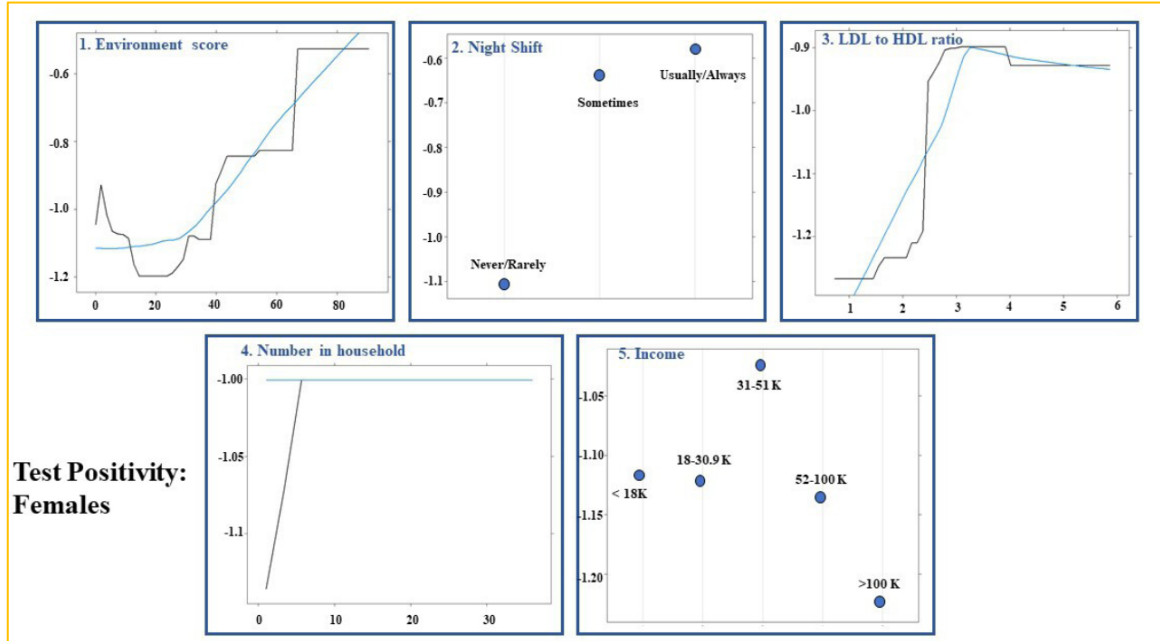
AIM: We explored the **ASSOCIATION BETWEEN SEX, GENDER, AND CARDIOVASCULAR HEALTH (CVH)** amongst Canadian (CAN) and Austrian (AT) populations.
Study Populations: Canadian Community Health Survey (CCHS-2014) (n=63,522, 55% Females, 42.3% younger than 50 years) vs Austrian Health Interview Survey (AT-HIS-2014) (n=15,771, 56% Females, 53.86% younger than 50 years).

	Canadians 			Austrians 		
PREDICTORS OF HEART DISEASE	Odds Ratio (OR)	95% CI	P-value	Odds Ratio (OR)	95% CI	P-value
CANHEART score (Canadians) ATHEART score (Austrians)	0.73	0.71, 0.75	<0.001	0.77	0.69, 0.86	<0.001
Gender score	3.87	2.71, 5.52	<0.001	22.14	7.28, 68.17	<0.001
Sex (Female)	0.58	0.54, 0.62	<0.001	0.61	0.46, 0.82	0.002
Age groups						
<20 (reference)	-	-	-	-	-	-
20-29	0.95	0.62, 1.48	0.96	0.94	0.2, 4.42	0.70
30-39	0.70	0.45, 1.1	0.12	0.32	0.07, 1.67	0.08
40-49	1.82	1.26, 2.68	0.001	0.53	0.16, 2.38	0.21
50-59	4.62	3.34, 6.60	<0.001	2.14	0.77, 8.91	0.34
60-69	8.78	6.38, 12.47	<0.001	3.95	1.44, 16.36	0.04
>=70	19.45	14.16, 27.59	<0.001	7.28	2.32, 26.00	0.001

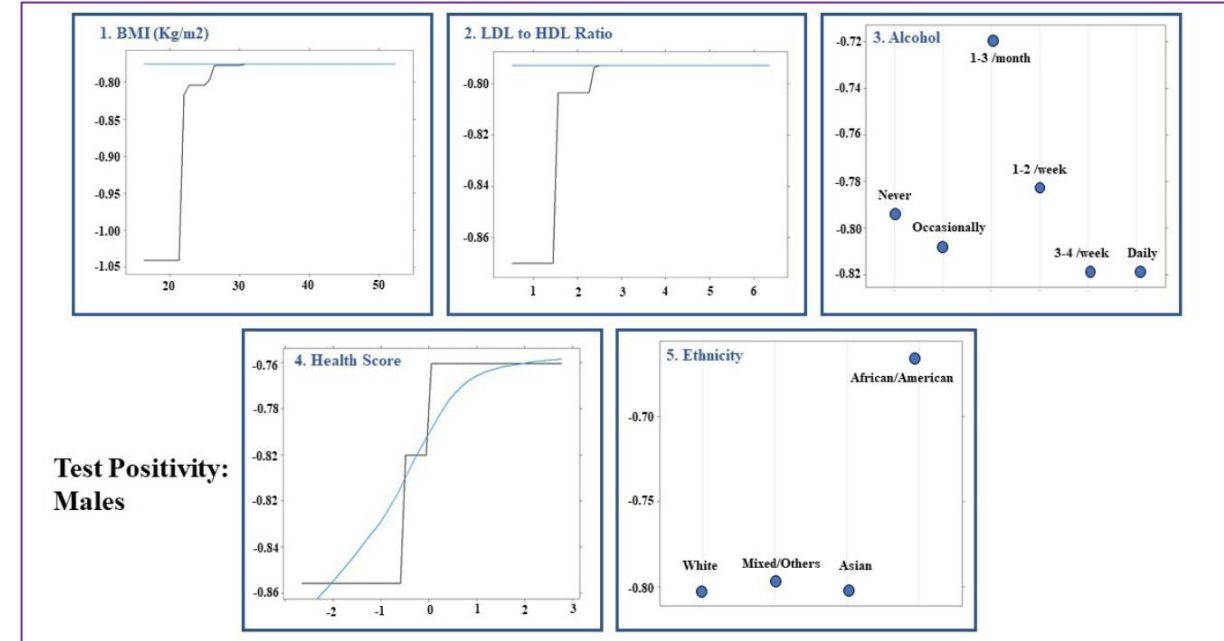
Machine learning-based prediction models for SARS-CoV-2 positive test



Of **4510** patients (51.2% females, and **68.5±8.88** years) who were tested in the UK-Biobank, **29.4% were positive**.
Females were less likely to be positive (males: 31.6% vs females: 27.3%, $p=0.001$).



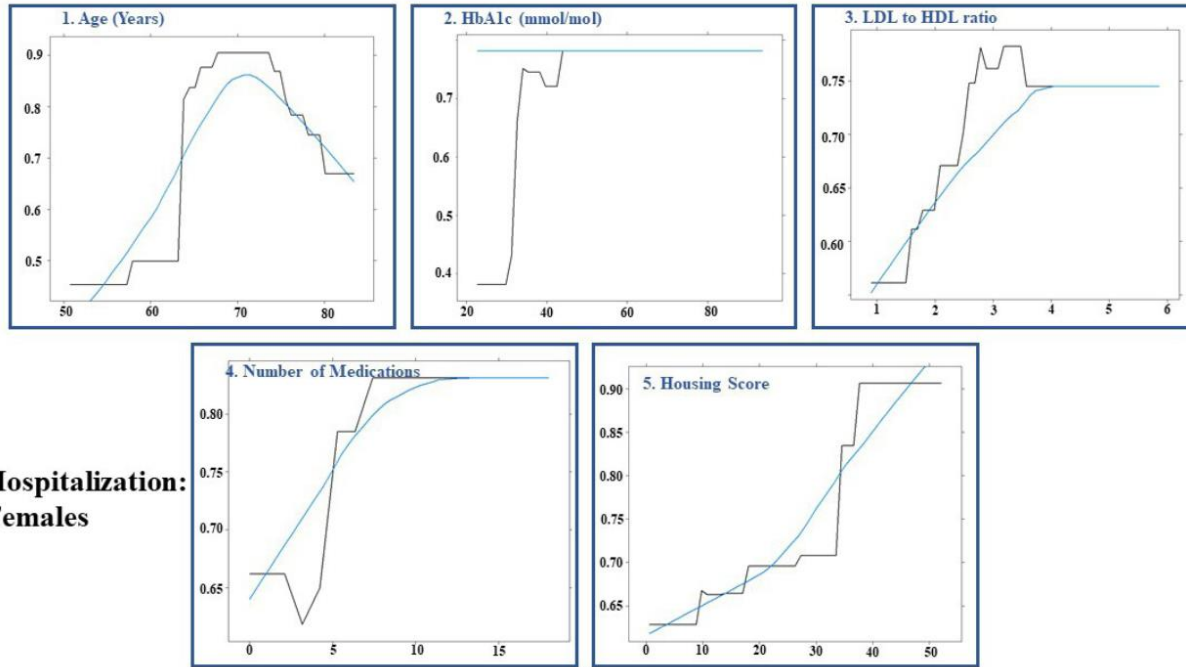
Females who lived in **more deprived areas** (increased environment score), had increased LDL/ HDL, **worked night shifts** and had a **greater number of family members** in their household, those with **lower income** were more likely to test positive.



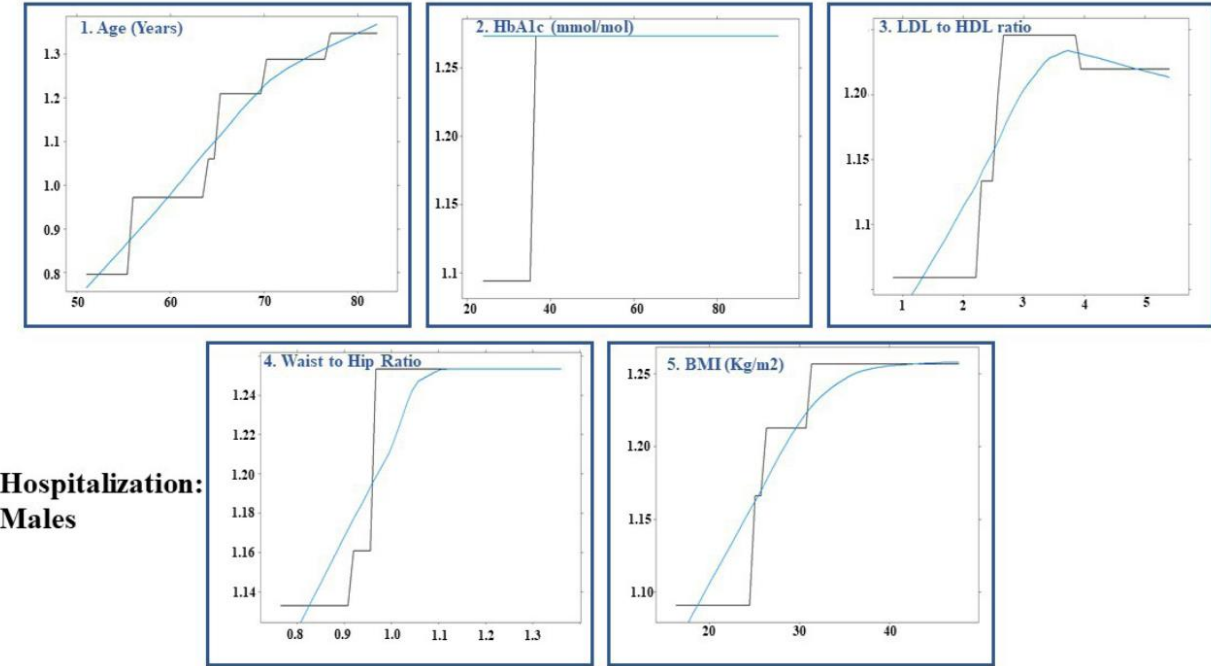
Males with **greater BMI** and **LDL to HDL ratio**, **more deprived area** (greater score) and **black British ethnicity** were more likely to test positive



Among the **1326 test-positive** patients, **932 (70.3%)** were hospitalised (females: 44.3%).



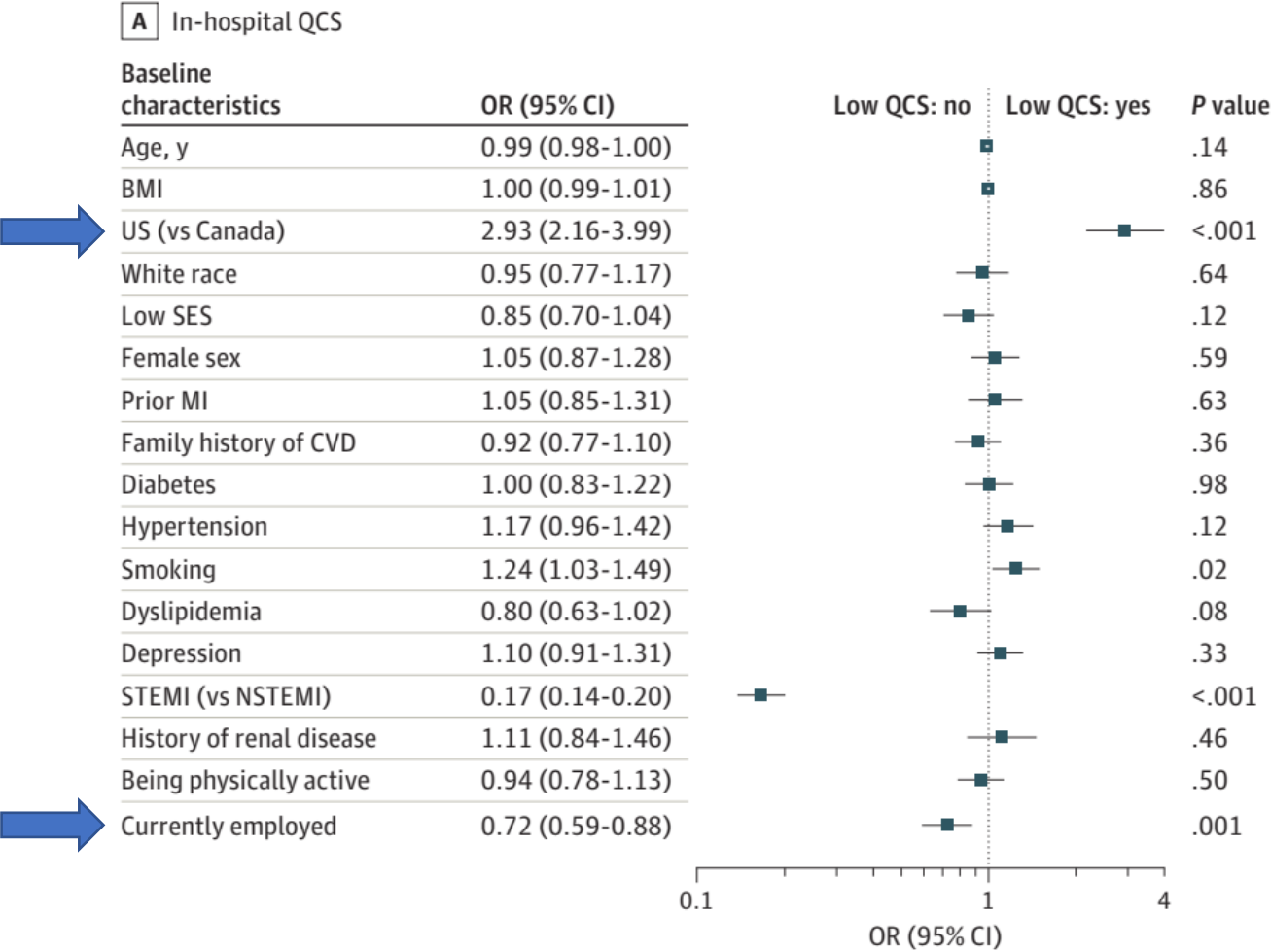
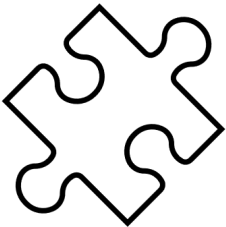
Older age, a higher level of HbA1c, LDL to HDL ratio, a greater number of medications and higher housing score (showing more deprived areas) were most influential in females

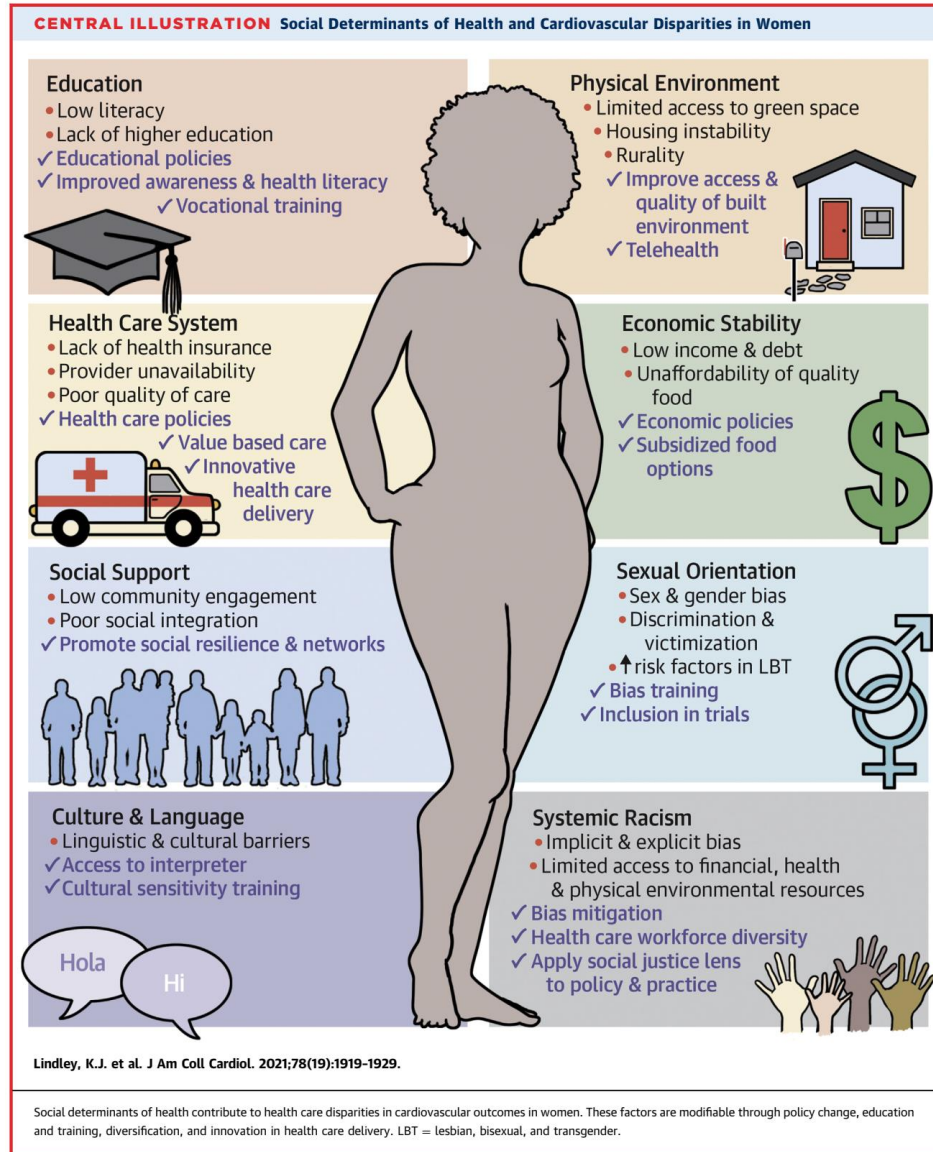


Older age, an increased HbA1c level, WHR, LDL to HDL ratio and BMI were the most influential variables in males

Variations in Quality of Care by Sex and Social Determinants of Health Among Younger Adults With Acute Myocardial Infarction in the US and Canada

Valeria Raparelli, MD, PhD; Louise Pilote, MD, MPH, PhD; Brian Dang, MDCM; Hassan Behloul, PhD; James D. Dziura, PhD, MPH; Hector Bueno, MD, PhD; Gail D'Onofrio, MD; Harlan M. Krumholz, MD, SM; Rachel P. Dreyer, PhD

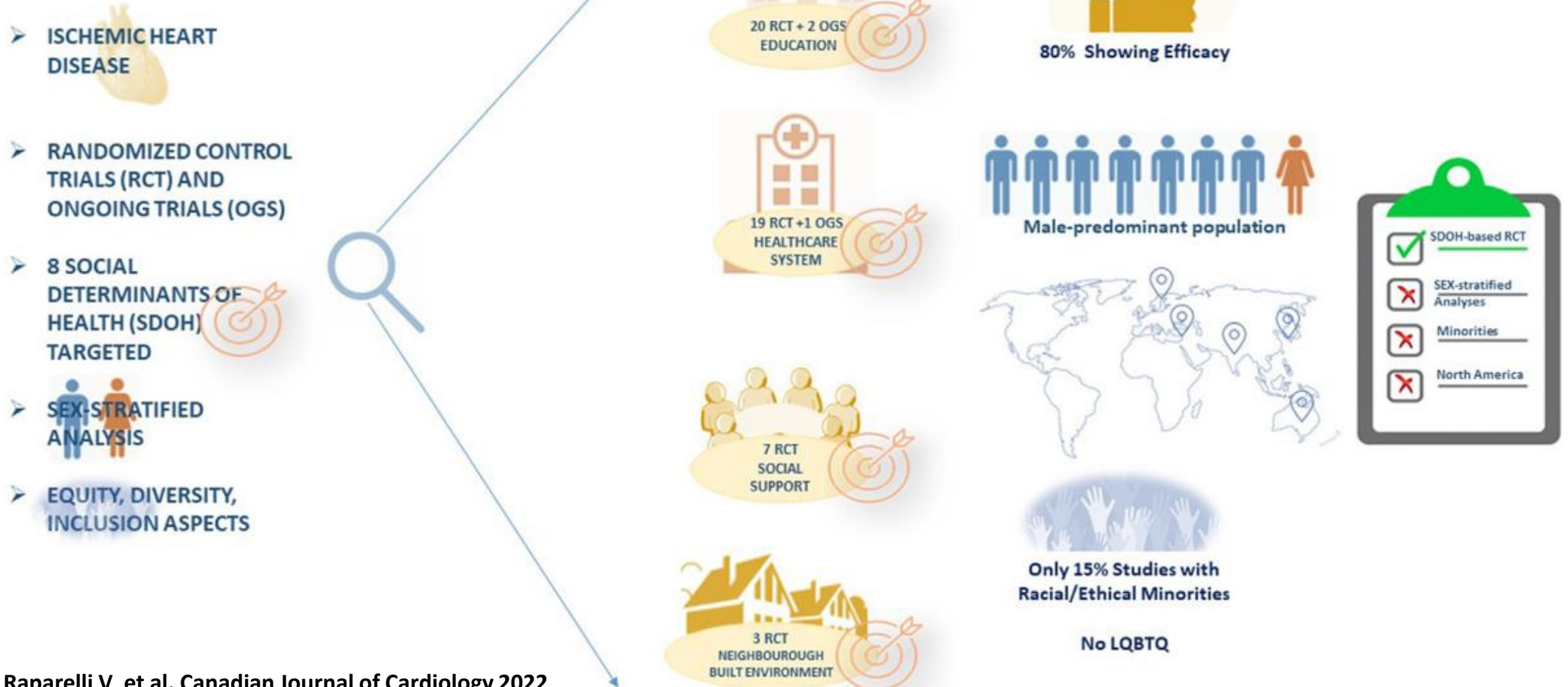




HIGHLIGHTS

- In addition to biological differences, socioeconomic factors contribute to disparities in cardiovascular health outcomes in women, and many are potentially modifiable.
- Key factors contributing to health care disparities include poverty, racism, geography, education and access to health care insurance.
- Overcoming disparities that affect the cardiovascular health of women include policy changes, education and training, innovations in health care delivery, and diversification of the cardiology workforce.

Interventions Targeted to Address Social Determinants of Health in Ischemic Heart Disease: A Sex- and Gender-Oriented Scoping Review





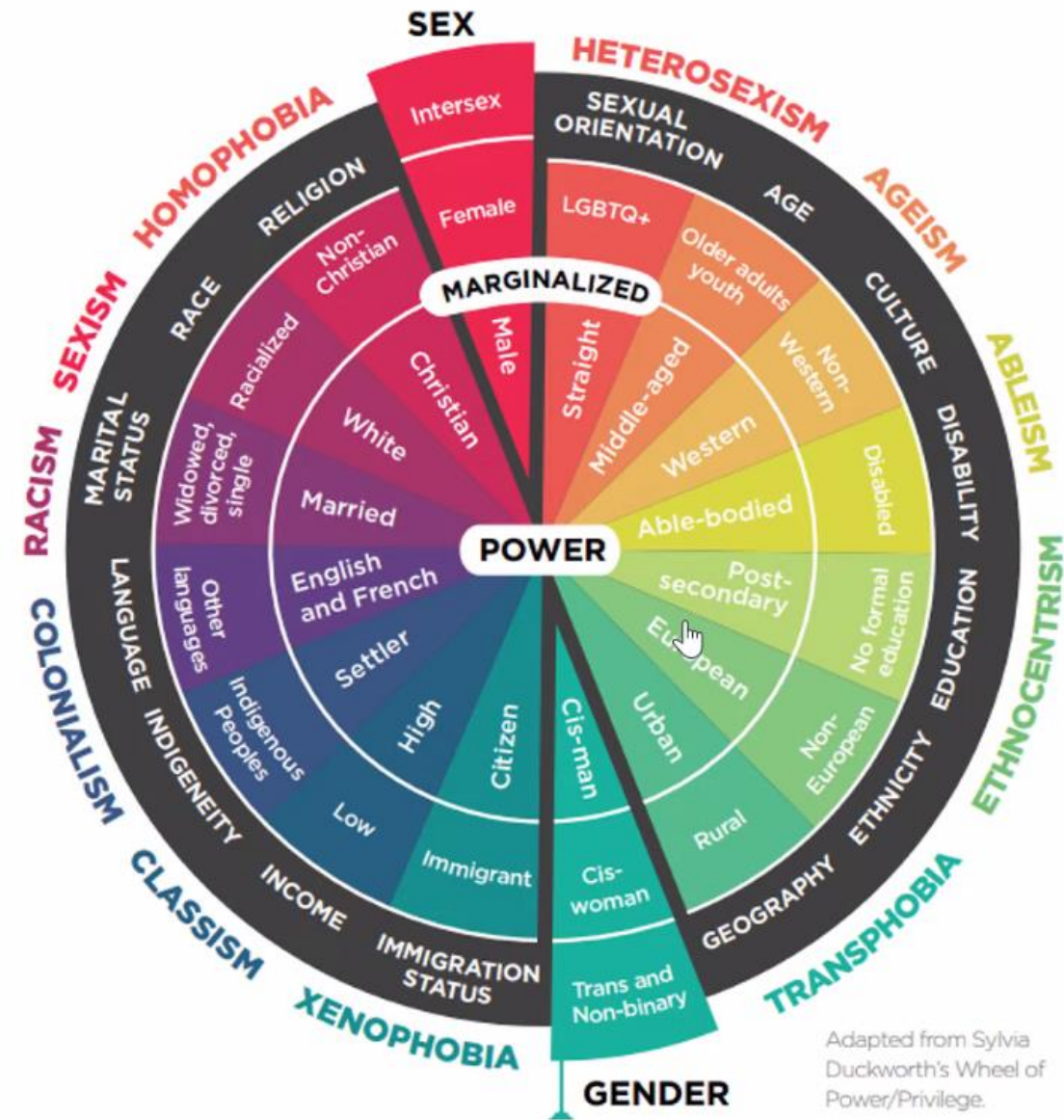
WHAT'S
NEXT





Intersectionality

Intersectionality is a theoretical framework rooted in the premise that human experience is jointly shaped by multiple social positions (e.g. race, gender), and cannot be adequately understood by considering social positions independently.



Bauer Greta, Quantitative intersectional study design and primary data collection. Meet the methods series, Canadian Institutes of Health Research, 2021.

1. INDIVIDUAL OBSERVATIONS AND SELF-REFLECTION BASED ON AN ENCOUNTERED CLINICAL CASE

Briefly describe a clinical case encountered during the internship: ...

Anamnesis: Would the anamnesis have been different if the patient had been of the opposite gender?

☐ Yes ☐ No

Clinical exam: would the clinical exam have been different if the patient had been of the opposite gender?

☐ Yes ☐ No

Differential diagnosis: Would the differential diagnosis assumptions have been different if the patient had been of the opposite gender?

☐ Yes ☐ No

Management: Would the proposed diagnostic and/or therapeutic measures have been different if the patient had been of the opposite gender?

☐ Yes ☐ No

Using your previous answers, describe for each step related to the clinical consultation (anamnesis, etc.) the elements that support an identical or different approach depending on the gender of the patient:

2. COLLECTIVE REFLECTION

Following the group session, are there any important points (agreement or disagreement) that were raised from your presented clinical case?

3. PERSONAL SYNTHESIS AND SELF-REFLECTION

What are the most important elements I have learned?

What aspects have been most difficult for me?

What will I integrate into my medical practice?

Gender Reflexivity in clinical practice



Medical neutral positionality does not exist

-> *Medical Practice as a social relation with actors that are situated in a social context*

To minimize the detrimental effects of stereotypes and bias

-> *Identify, Acknowledge, Discuss, Control them with reflexivity in medical clinical reasoning*



Universität
Zürich



Geiser E, Schilter LV, Carrier JM, Clair C, Schwarz J. Reflexivity as a tool for medical students to identify and address gender bias in clinical practice: A qualitative study. Patient Educ Couns. 2022 Dec;105(12):3521-3528.

The SIMI Gender '5 Ws' Rule for the integration of sex and gender-related variables in clinical studies towards internal medicine equitable research



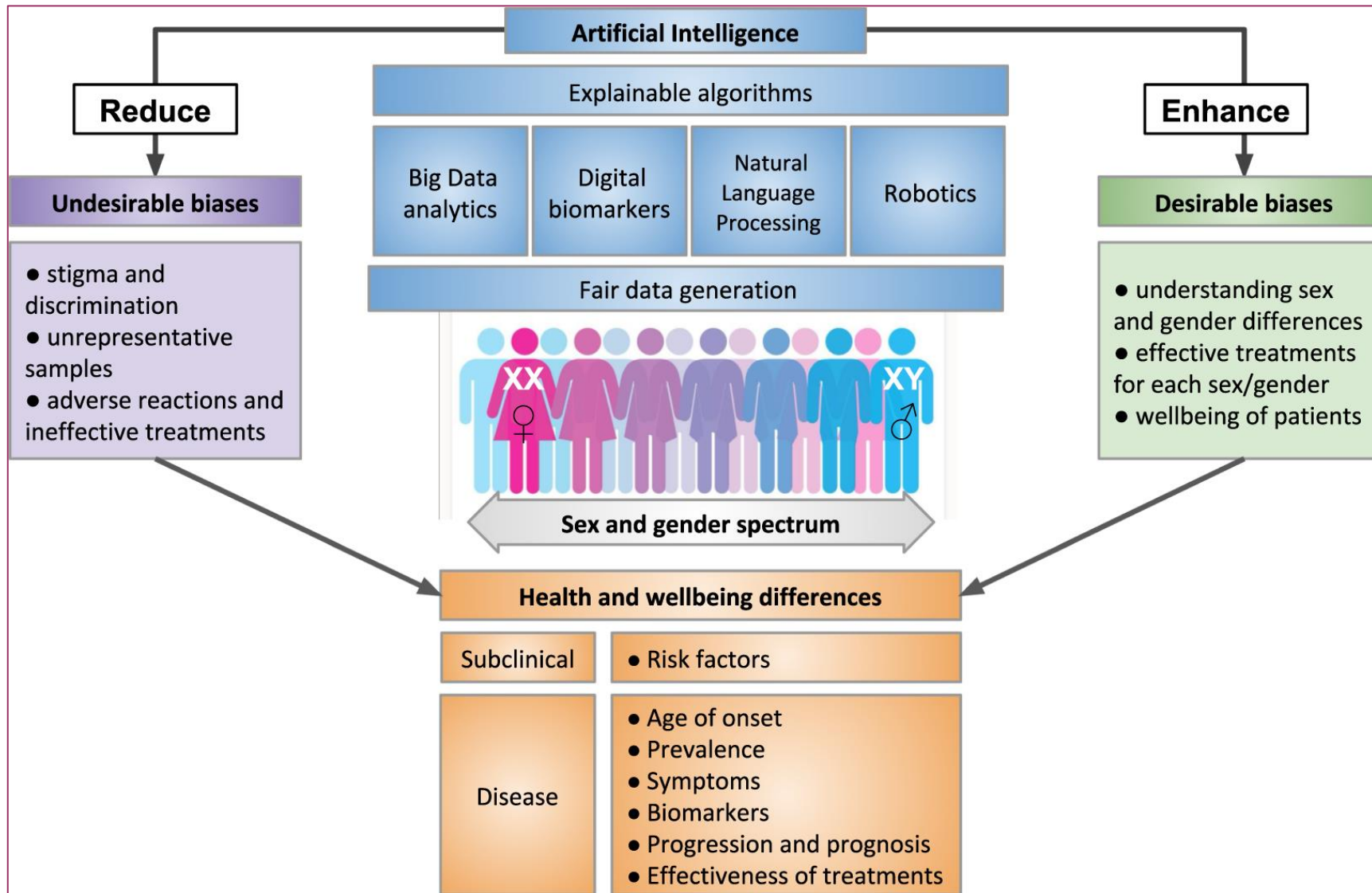
**The
SIMI
Gender**



**'5 Ws'
Rule**



Raparelli V, et. Intern Emerg Med. 2022 Oct;17(7):1969-1976.



Fair data generation and explainable algorithms are fundamental requirements for the design and application of artificial intelligence to optimize for health and wellbeing across the sex and gender spectrum. This will facilitate the reduction of undesirable biases that propagate inequity and discrimination, and will promote desirable differentiations that help develop Precision Medicine.