Considering Multimorbidity and Chronic Debilitating Conditions in Women

Chronic Debilitating Conditions in Women

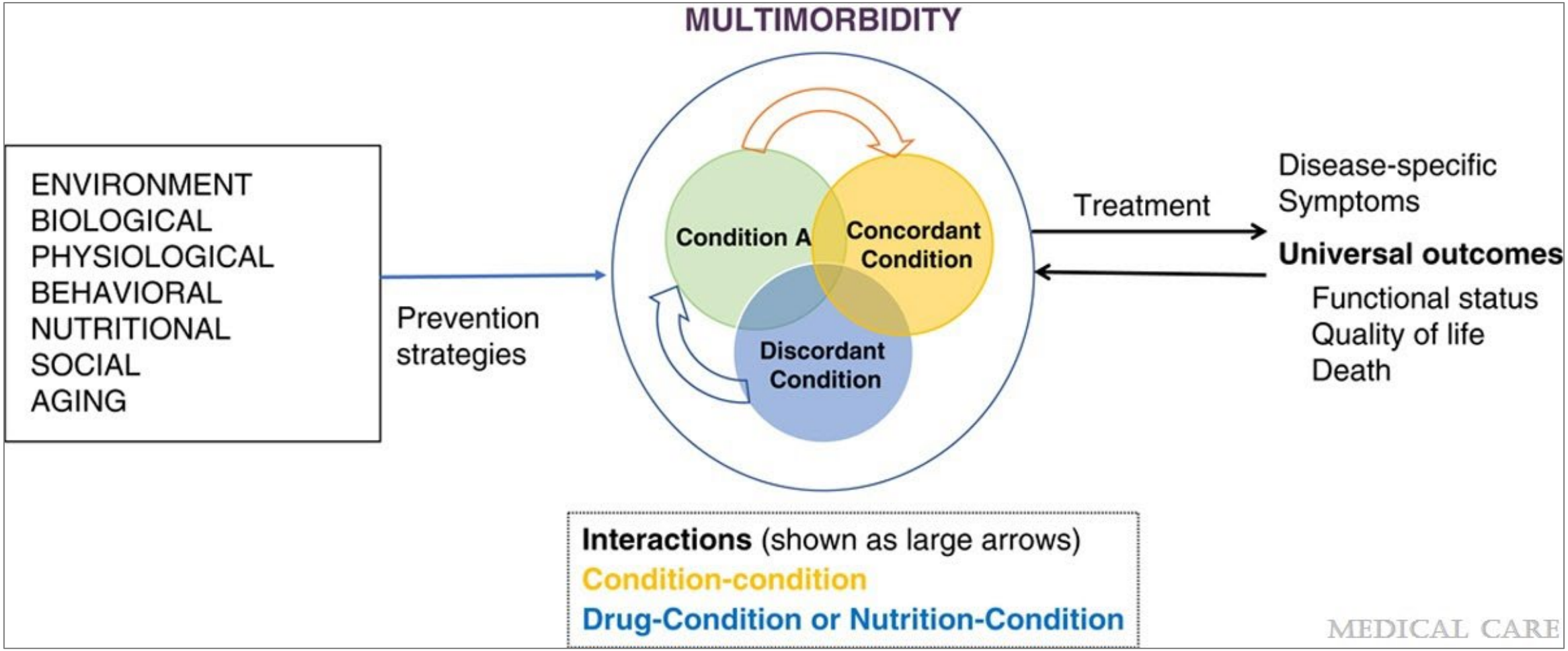
Impact on women	Condition (2019 Disability-associated Life Years lost)					
Higher incidence and/or morbidity	**Depressive Disorders** **(1,704,524)**	**Migraine/ Headache** (1,573,325)	**Breast cancer** (1,387,670)	**Rheumatoid Arthritis** (187,902)	**Multiple Sclerosis** (143,123)	**Autoimmune diseases**
Notably high morbidity	**Heart Disease** **(3,396,660)**	**Lower back pain** (3,168,583)	**COPD** **(2,568,947)**	**Substance Use Disorders** **(2,323,237)**	**Stroke** **(2,098,900)**	**Diabetes** **(2,010,853)**

Adapted from Women's Health Consensus Report, 2021
*Per MCS-WH reporting guidance, the following RCDC disease categories are particularly relevant to women's health

http://www.healthdata.org/

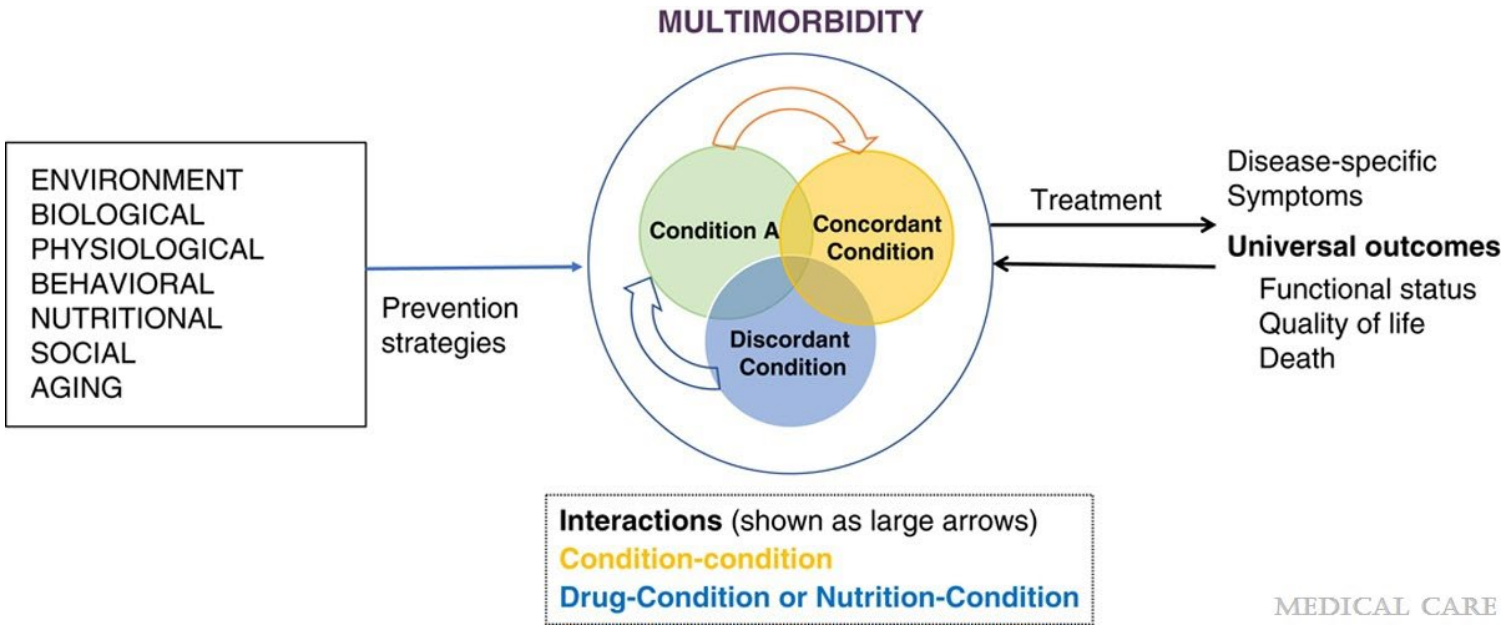
- 30% increase (2005-2014) in suicide for adolescent girls and young women
- 260% increase (1999 – 2017) in death rate from drug overdose in women
- 25% increase (2013-2018) in heart disease-related deaths in women aged 18-44

Conceptual Model of Multimorbidity (Office of Disease Prevention)



National Institutes of Health Advancing Multimorbidity Research Salive, Marcel E.; Suls, Jerry; Farhat, Tilda; Klabunde, Carrie N., Medical Care59(7):622-624, July 2021. doi: 10.1097/MLR.000000000000156

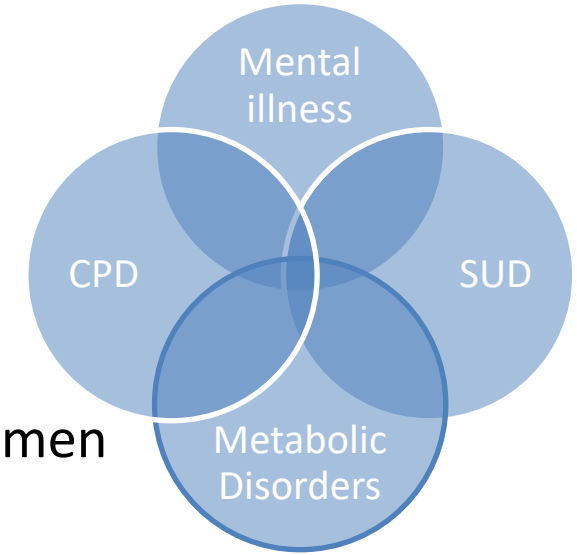
Chronic Debilitating Conditions and Multimorbidity



- Multimorbidity is *common* in chronic conditions
  - Comprises significant % of patients with chronic debilitating conditions
  - Can have developmental origins
  - Prevalence and severity increases across the lifespan

- National Institutes of Health Advancing Multimorbidity Research Salive, Marcel E.; Suls, Jerry; Farhat, Tilda; Klabunde, Carrie N., Medical Care59(7):622-624, July 2021. doi: 10.1097/MLR.000000000000156

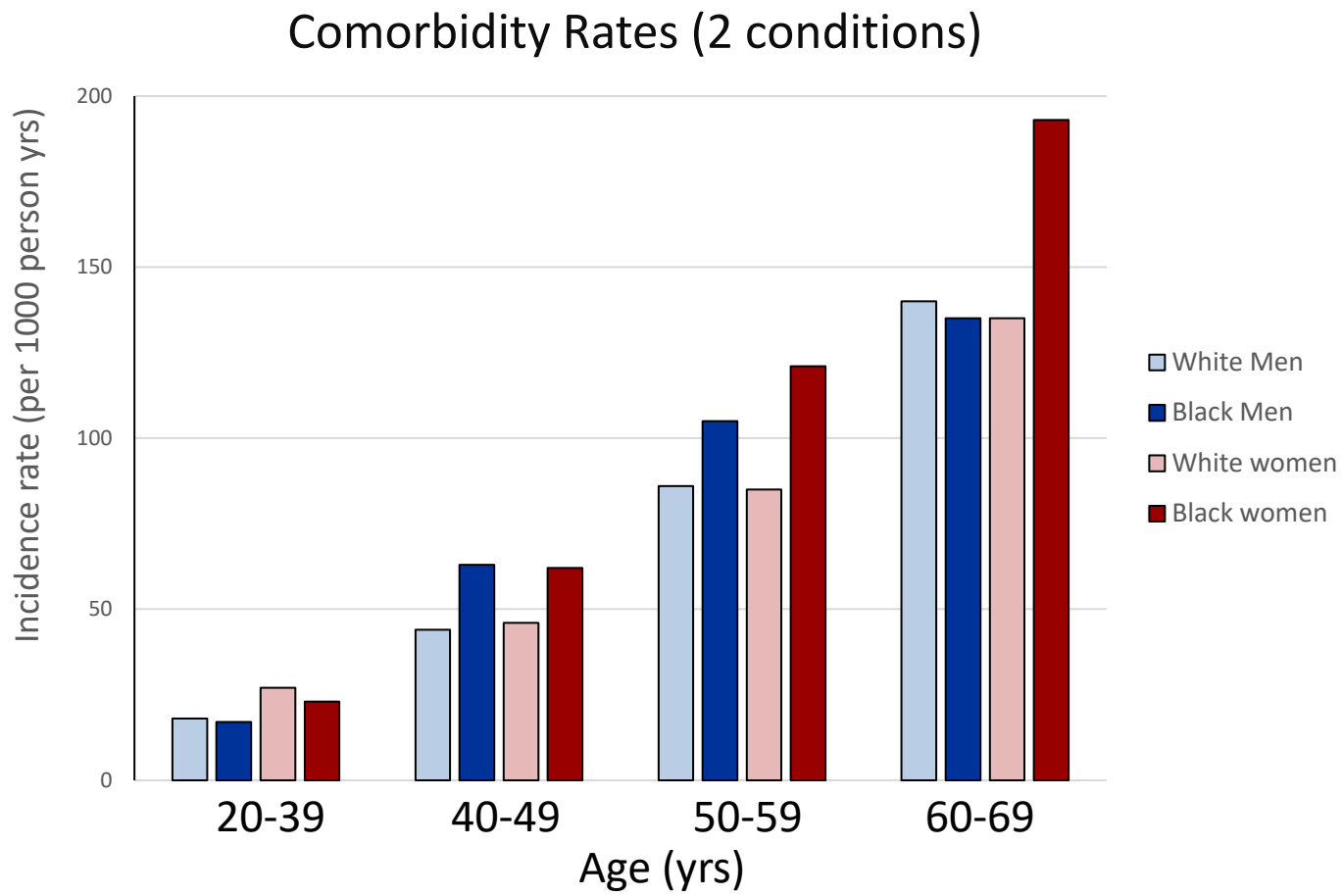
Multimorbidites common in women (selected findings)



- Higher comorbidity of diabetes and thyroid dysfunction with cardiovascular disease (CVD)
- Asthma-obesity comorbidity specific to girls/women
- Higher ADHD-Asthma comorbidity
- 2x the risk of comorbidity of Major Depressive Disorder and CVD
  - Women with longer history/more severe MDD show 3-fold the risk for CVD related clinical events and death
- Cardiovascular disease (CVD) comorbidity highest in women with
  - History of trauma
  - Severe mental illness
  - Chronic misuse of alcohol, cigarettes, psychostimulants
- More rapid progression of chronic alcohol-associated cardiovascular conditions (telescoping)

Sources : Stewart et al. 2017 ; Goldstein et al, 2018; Women's Ischemia Syndrome Evaluation (WISE); Dana E. King, Jun Xiang, Courtney S. Pilkerton. *JABFM* 2018, 31 (4) 503-513; Sharma & Balhara, *J Social Health and Diabetes*, 2016; Bancks et al, *Diabetologia*. 2015; Walter et al, *Current Diabetes Reports*, 2017

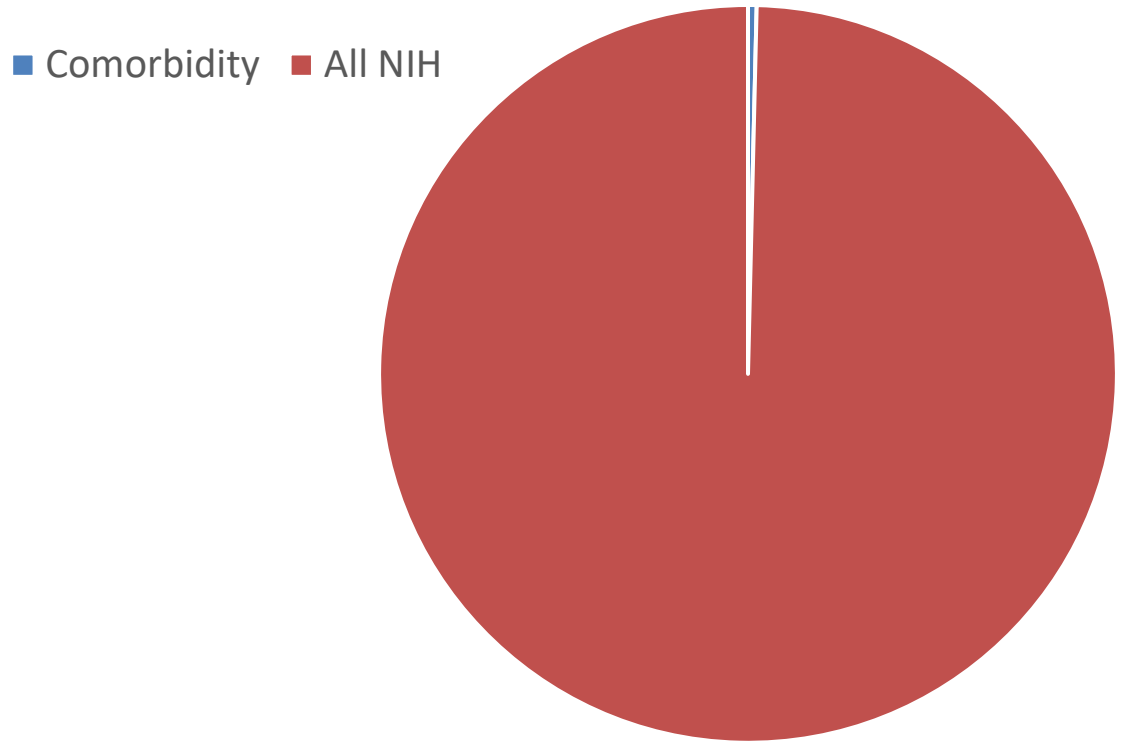
Multimorbidities disproportionately impact BIPOC Women



Multimorbidities are understudied and undertreated in BIPOC women

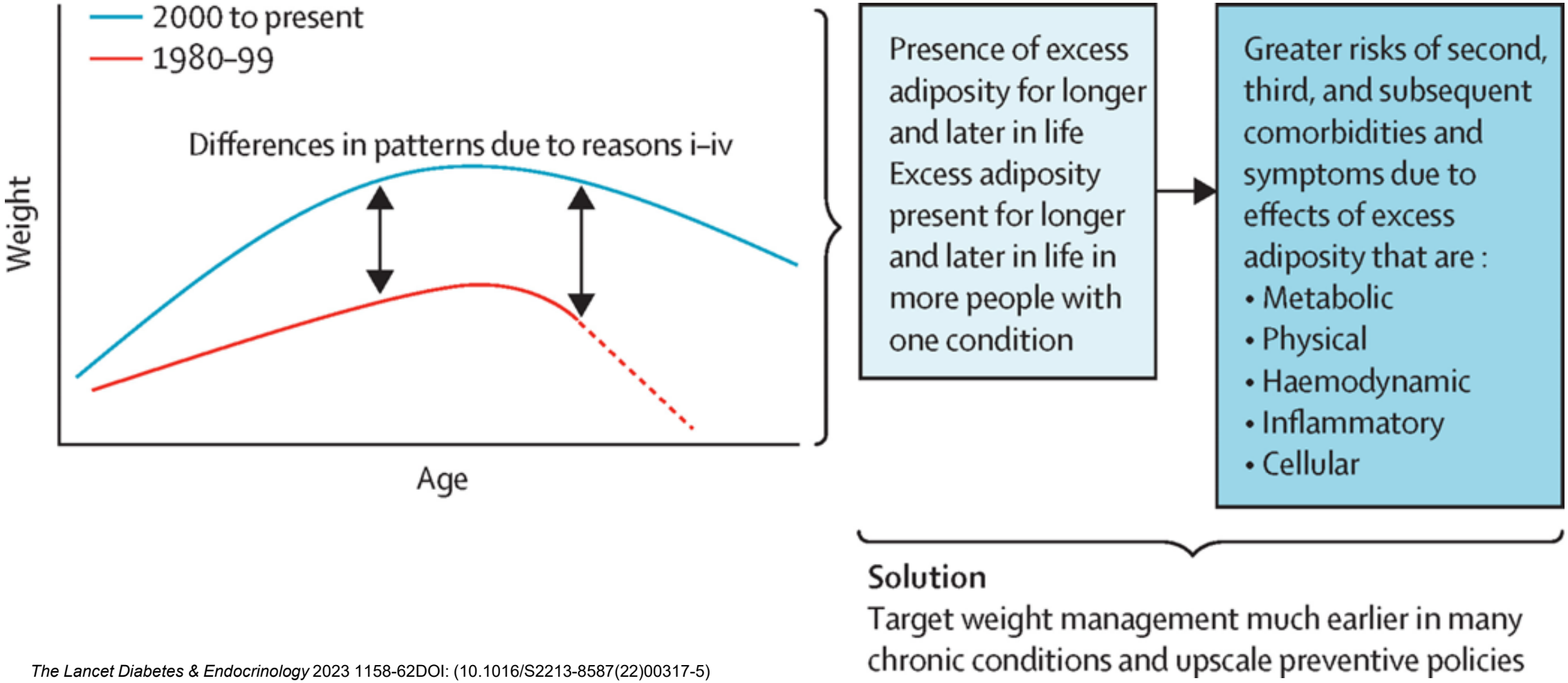
Source: St Sauver JL, Boyd CM, Grossardt BR, et al. *BMJ Open.* 2015.

Multimorbidity is systematically understudied



Sex and Gender Differences in Multimorbidity are Woefully Understudied

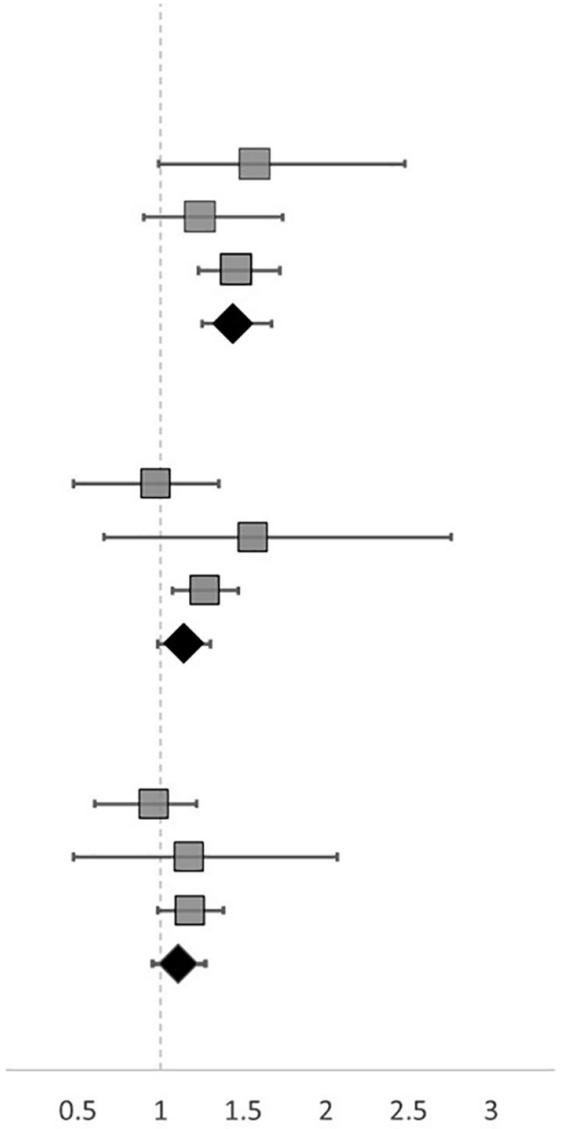
“Use case” – Comorbid metabolic disorders/obesity



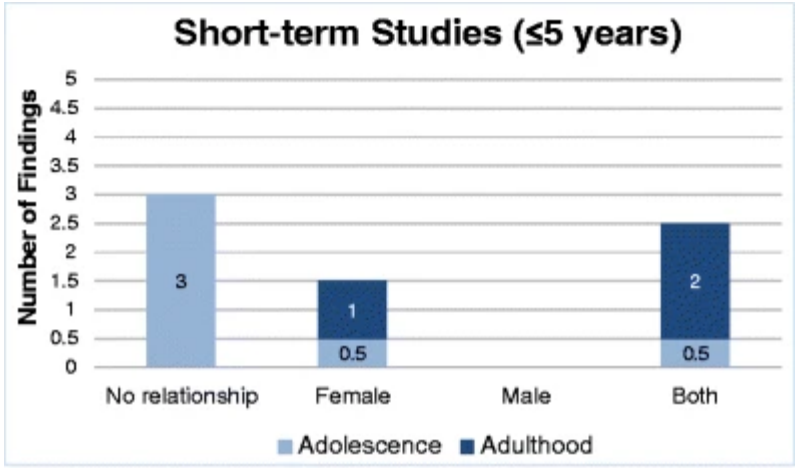
The Lancet Diabetes & Endocrinology 2023 1158-62DOI: (10.1016/S2213-8587(22)00317-5)

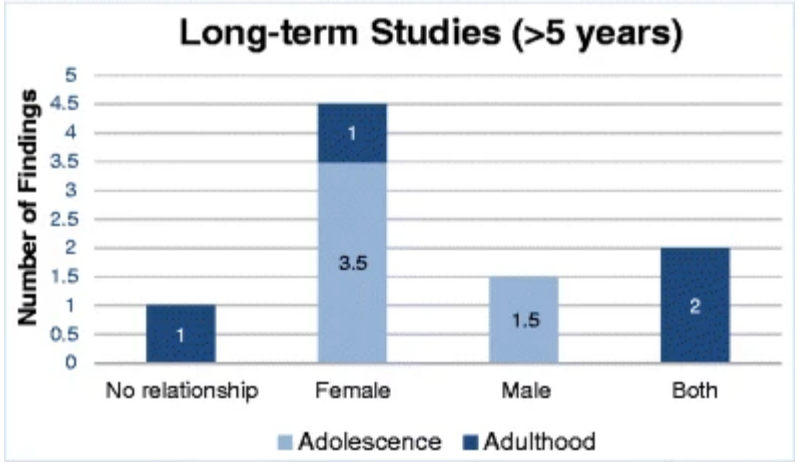
Association betwen sex and obesity in people with SMI

	Females		Males		
	Events	Total	Events	Total	O.R. [95% C.I.]
Obesity					
Any (n=8)	274	802	263	905	1.57 [0.99 - 2.48]
Bipolar disorders (n=4)	155	446	86	297	1.24 [0.90 - 1.86]
Schizophrenia (n=17)	3194	12834	3162	15746	1.46 [1.23 - 1.72]
Pooled OR (REM)		14082		16948	**1.44 [1.25 - 1.67]**
Heterogeneity: Isqr 72%, tsqr = 0.07, p < 0.01					
Overweight					
Any (n=7)	332	1238	474	1371	0.97 [0.59 - 1.68]
Bipolar disorders (n=3)	79	309	45	217	1.56 [0.74 - 3.30]
Schizophrenia (n=13)	1207	4357	1458	6387	1.27 [1.16 - 1.39]
Pooled OR (REM)		5904		7975	**1.14 [0.80 - 1.64]**
Heterogeneity: Isqr 72%, tsqr = 0.07, p...					
Overweight and obesity					
Any (n=7)	836	1238	952	1371	0.96 [0.70 - 1.32]
Bipolar disorders (n=3)	175	309	123	217	1.17 [0.60 - 2.17]
Schizophrenia (n=13)	2294	4357	3558	6387	1.18 [1.01 - 1.38]
Pooled OR (REM)		5904		7975	**1.11 [0.95 - 1.27]**
Heterogeneity: Isqr 71%, tsqr = 0.11, p...					

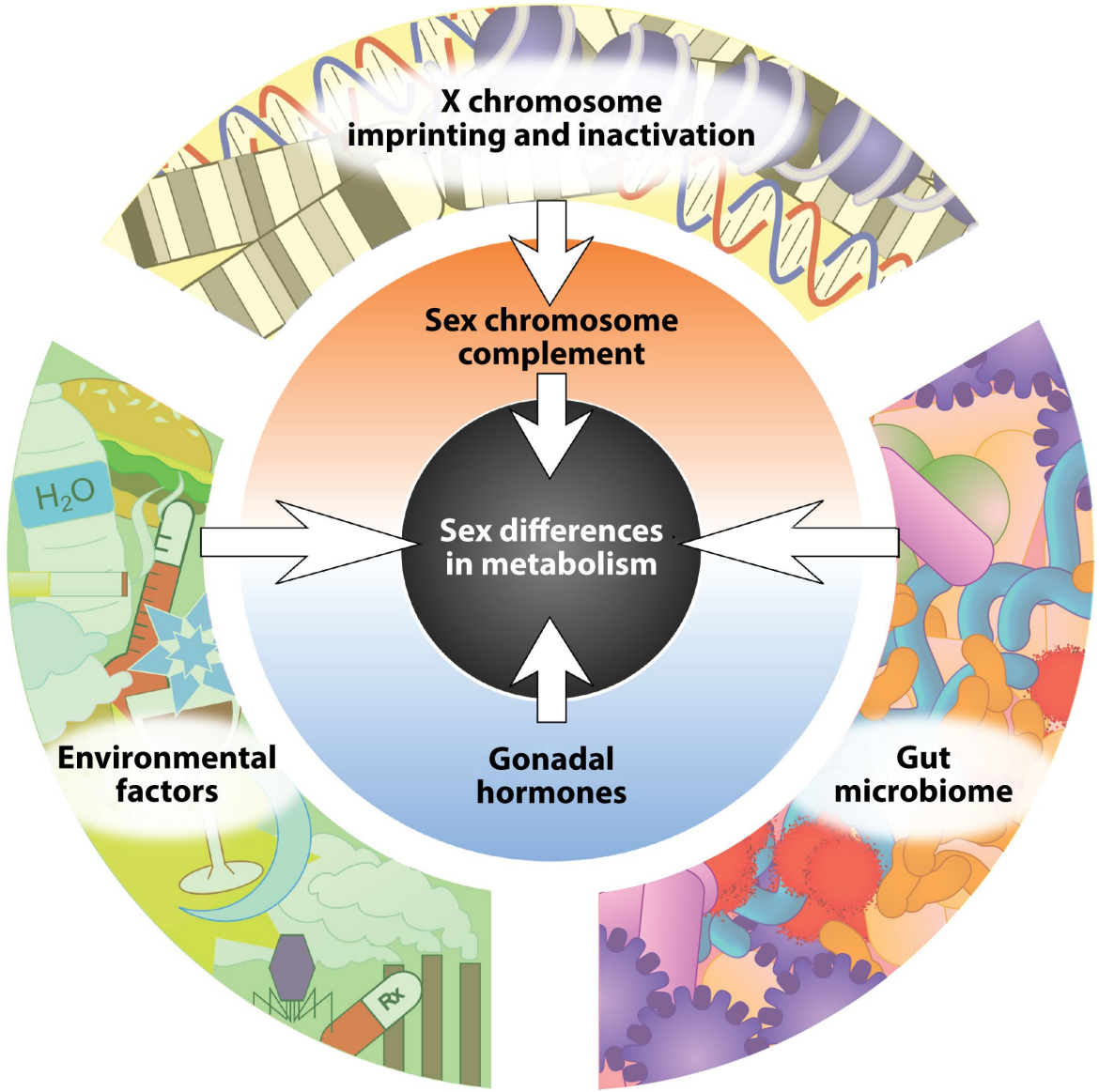


Developmental origins of sex/gender differences in complex morbidity Obesity and Major Depression

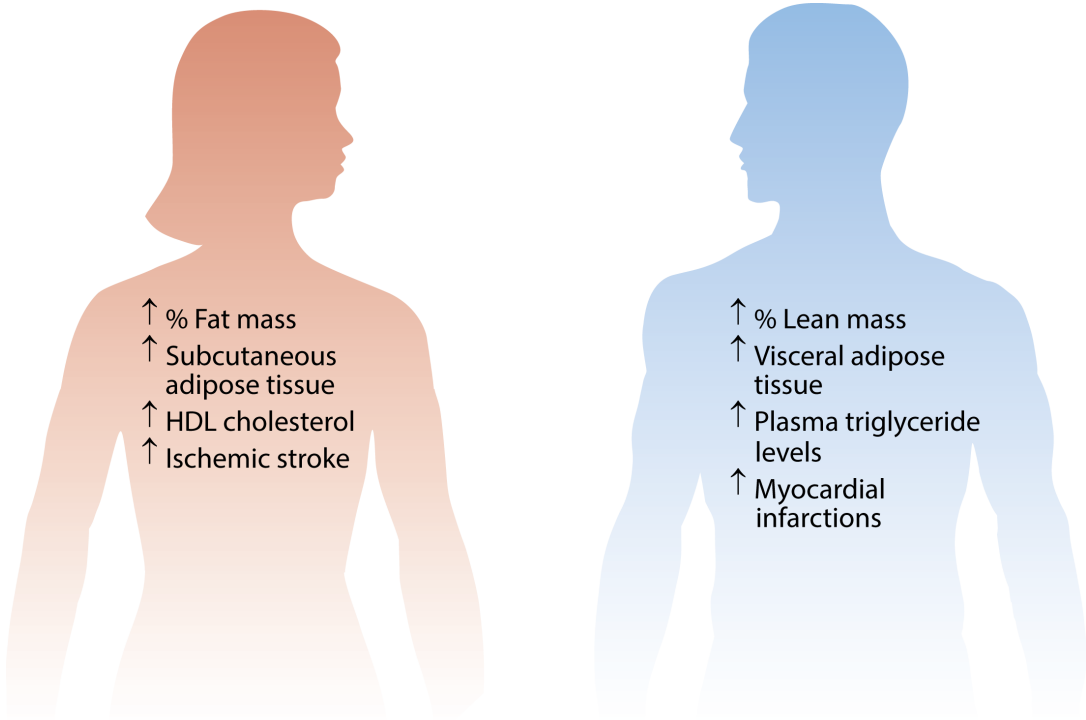




Tronieri, J.S., Wurst, C.M., Pearl, R.L. et al. Sex Differences in Obesity and Mental Health. Curr Psychiatry Rep 19, 29 (2017). https://doi.org/10.1007/s11920-017-0784-8



Link JC, Reue K. 2017.
Annu. Rev. Nutr. 37:225–45



Link JC, Reue K. 2017.
Annu. Rev. Nutr. 37:225–45

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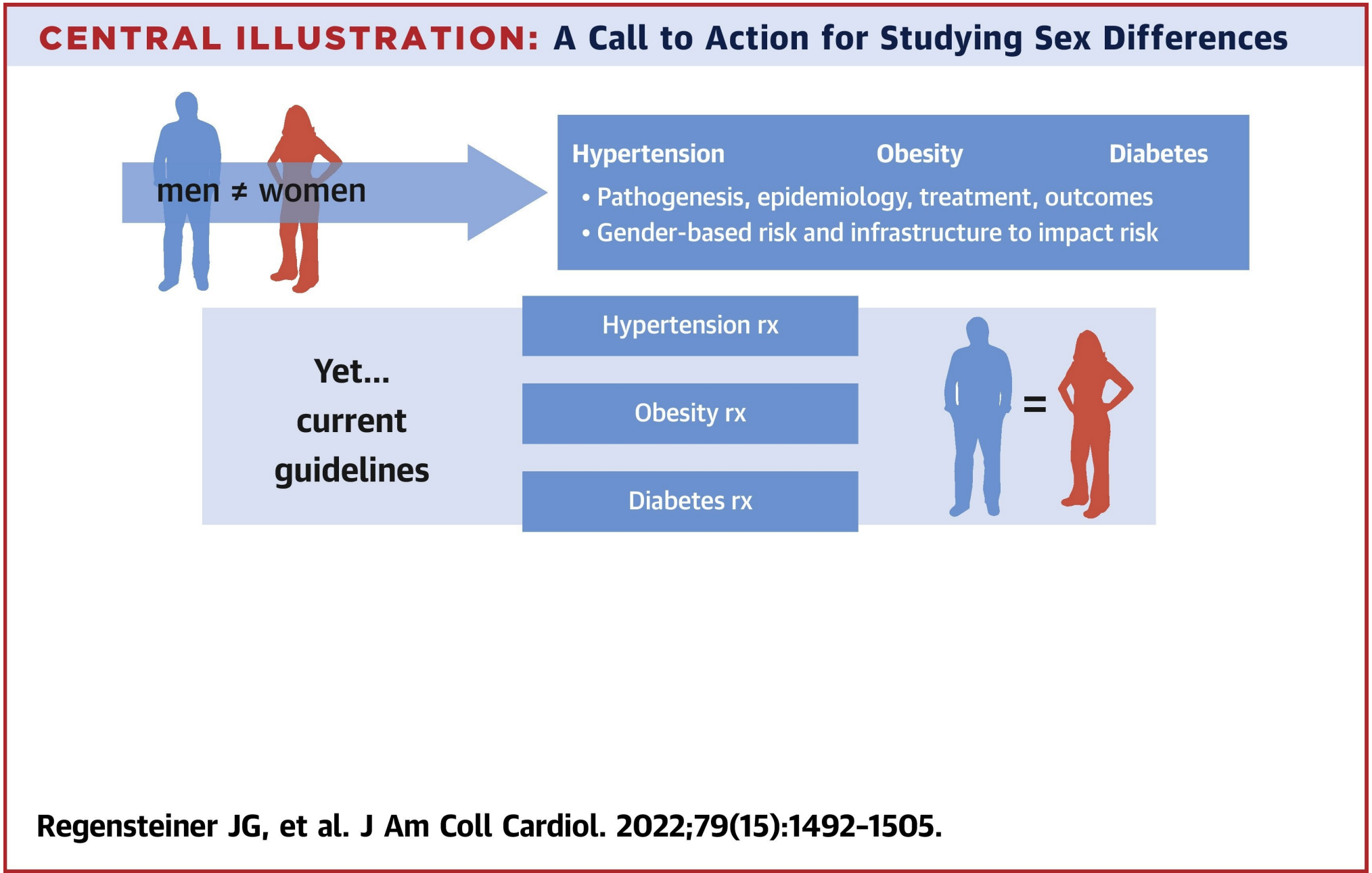
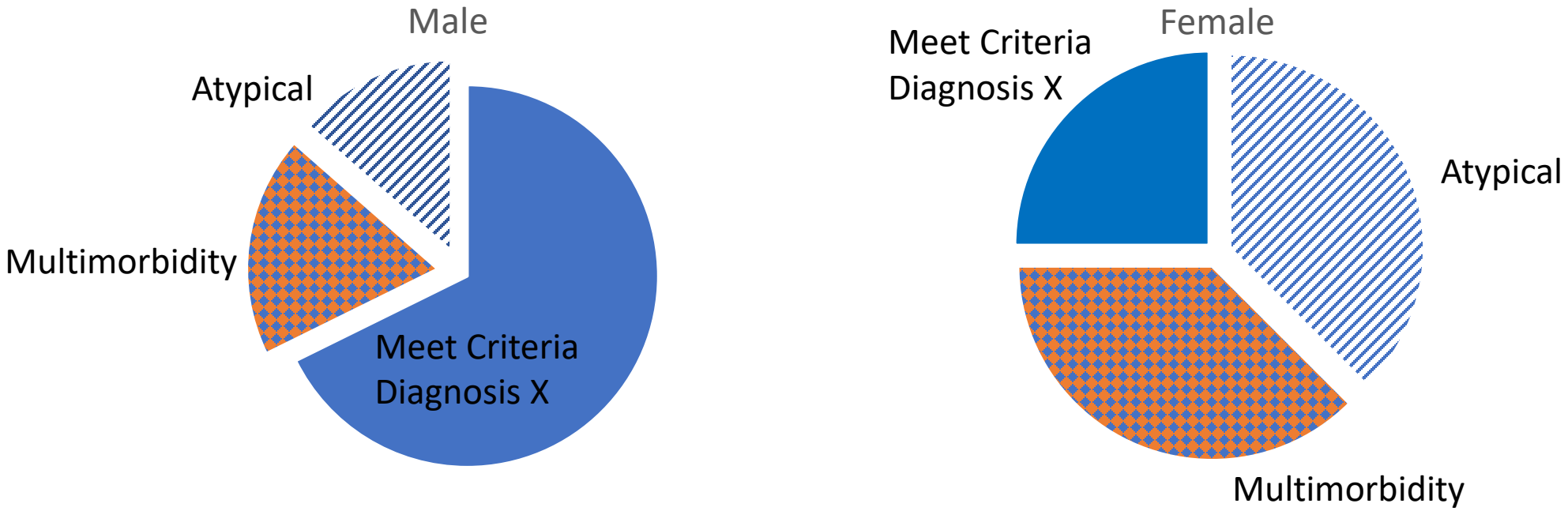
Evidence-based treatment without evidence



Regensteiner JG, et al. J Am Coll Cardiol. 2022;79(15):1492-1505.

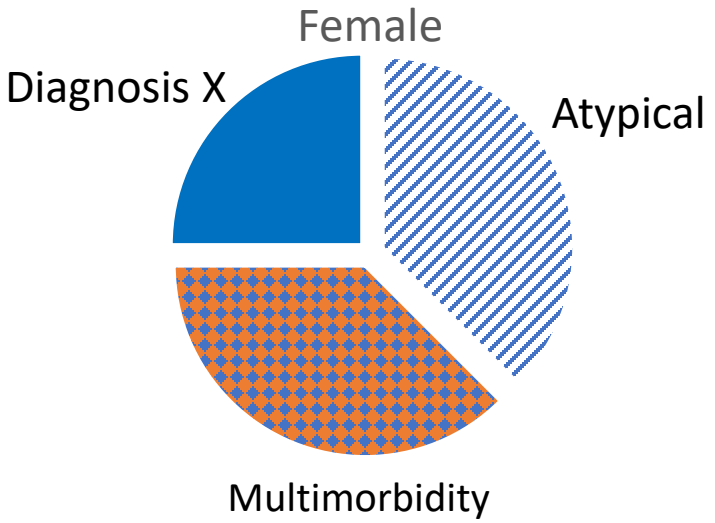
Gaps in Clinical and Translational Research:
Exclusion of subjects with multi-morbidities decreases the validity and generalizability of research throughout the pipeline



Discovery is “self-limited” : New data relevant to “single-diagnosis” population that we already know the most about

Exclusion of subjects with multi-morbidities decreases the validity and generalizability of research throughout the pipeline

Telescoping of ecologic validity and pathways to treatment



"Single-diagnosis" recruitment strategy leads to collection of data from a non-representative population

↓

Mechanisms underlying disease as it is manifested in "real world" patients, especially women, not studied

↓

Questions driving "translational" research, e.g. animal models, limited by findings from biased clinical research

→

Persistent Research Gaps

- Poor understanding of disease
- Limited/misdirected treatment development
- Limited/ineffective treatment options

Multimorbidity and Chronic Debilitating Conditions: Gaps in Research

Gaps in Study Design

- Rigorous measurement of multiple diseases and complex morbidity in epidemiological and mechanistic studies
- Longitudinal studies of disease processes and morbidity
- Inclusion of comorbidities in single-disease-focused studies
- Use of computational modeling incl. simulation to model complex morbidity

Intervention and Health Outcomes Research: *Person-centered approaches* incorporating

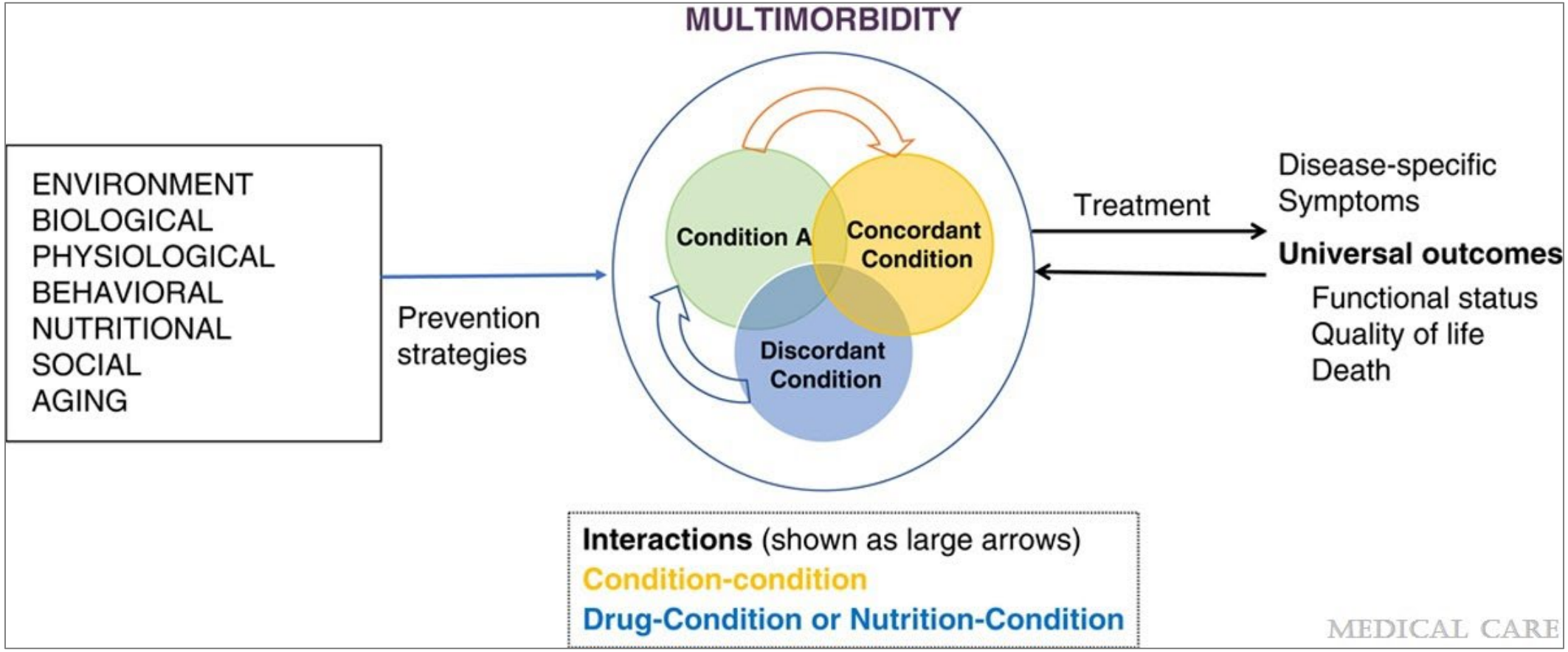
- biological and social context (age, sex, gender, dominant social factors)
- modeling of multimorbidity into learning healthcare systems
- integrated, continuum of care across primary care, geriatrics, disease specialties

National Institutes of Health Advancing Multimorbidity Research **Salive, Marcel E.; Suls, Jerry; Farhat, Tilda; Klabunde, Carrie N., Medical Care59(7):622-624, July 2021. doi: 10.1097/MLR.000000000000156**

Research to Prevent or Delay Development of Multimorbidity: An Analysis of the NIH Portfolio
Tilley DL, Dwyer JT, **Godette D,** Salive M, Suls J, **Vincent IS, Klabunde CN.** Poster presented at the 2020 Society for Prevention Research Annual Meeting, Online, July 21-23, 2020.

Addressing morbidity in NIH-funded research: Research on Multimorbidity

Conceptual Model of Multimorbidity (Office of Disease Prevention)



National Institutes of Health Advancing Multimorbidity Research Salive, Marcel E.; Suls, Jerry; Farhat, Tilda; Klabunde, Carrie N., Medical Care59(7):622-624, July 2021. doi: 10.1097/MLR.000000000000156

ODP Initiatives

- PAR-20-179: Advancing Research To Develop Improved Measures and Methods for Understanding Multimorbidity (R01 Clinical Trial Optional)

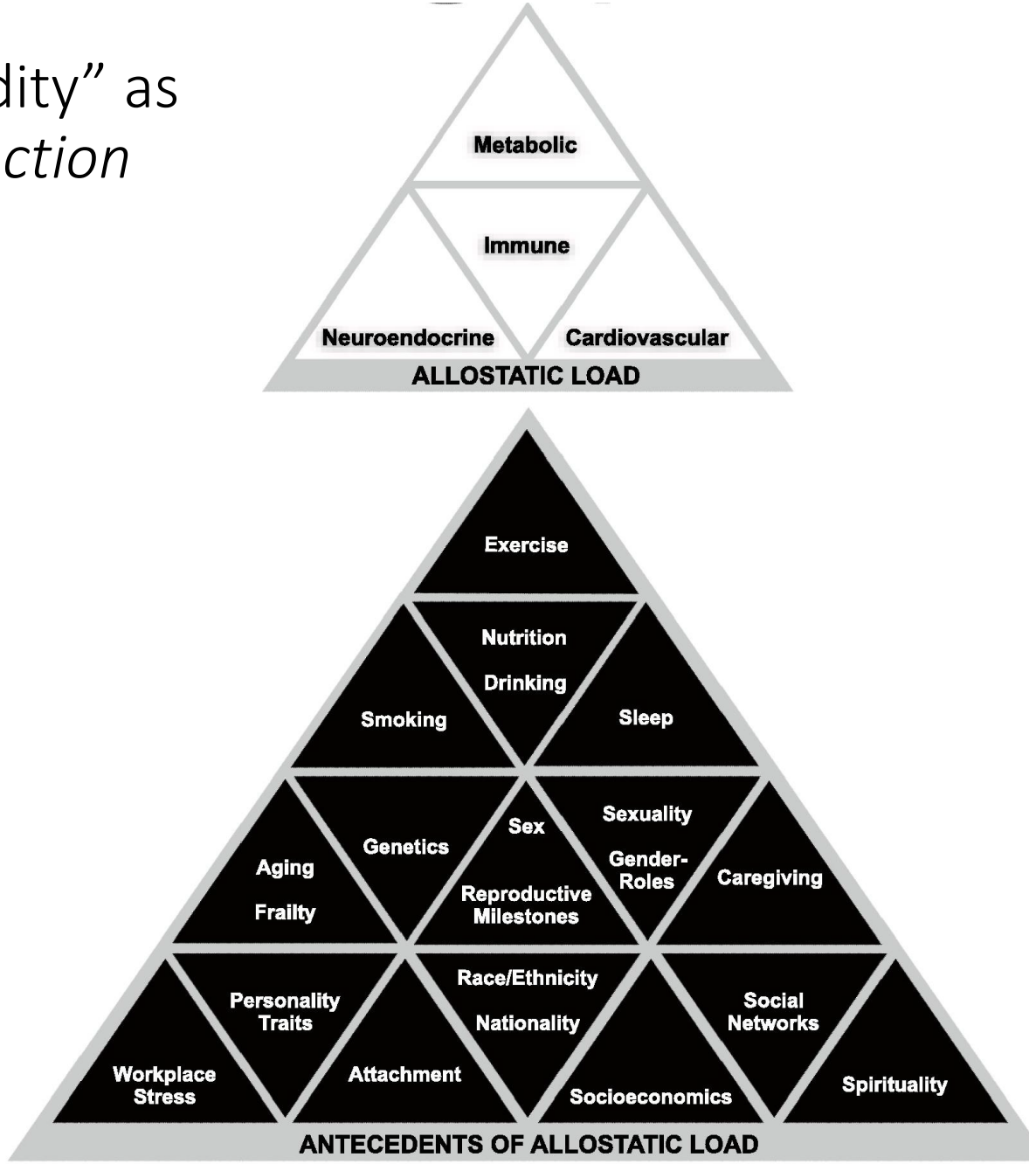
- PAR-20-180: Identifying Innovative Mechanisms or Interventions That Target Multimorbidity and its Consequences (R01 Clinical Trial Optional)

(last submission date Jan 2024)

Addressing morbidity in NIH-funded research: Translational and Clinical Research

Translational research: Studying “morbidity” as deviations along *integrated systems function*

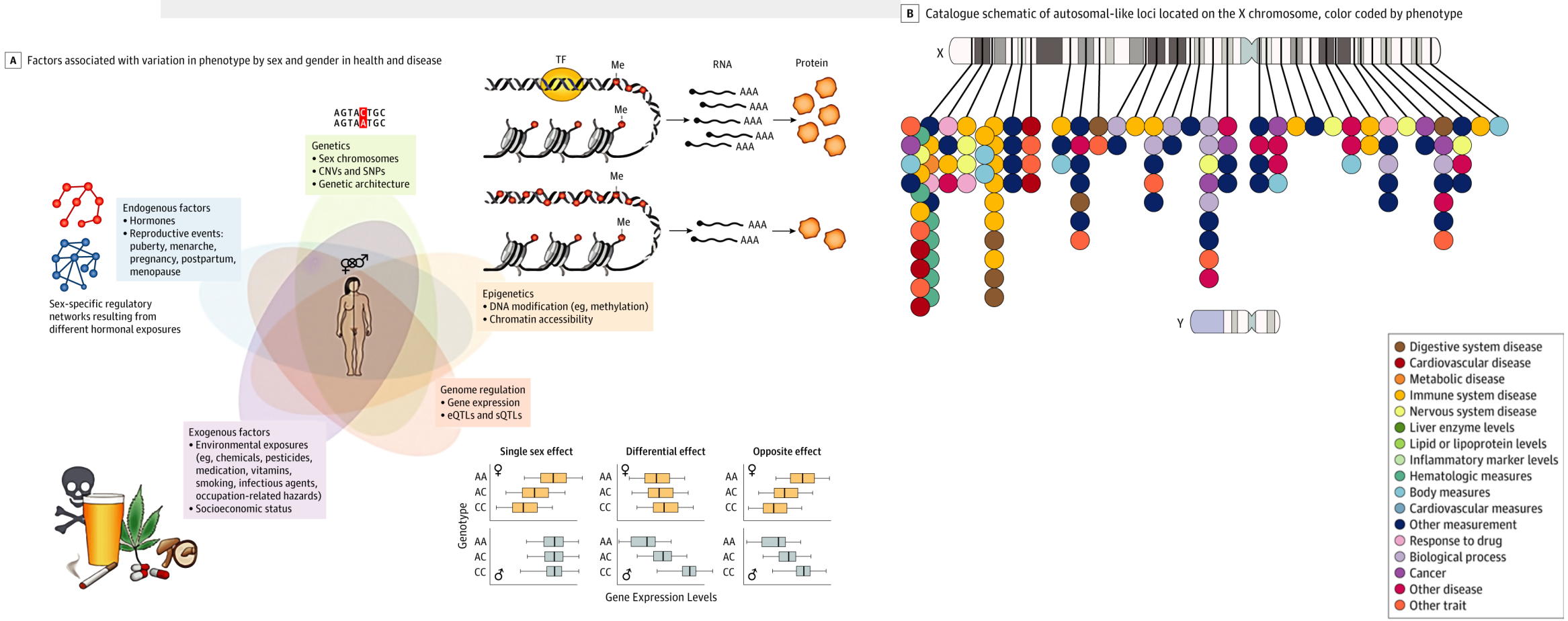
- Dimensions/Domains of function rather than the concept of diseases as discrete entities.
- Understanding how functional deviations in one system impact other systems

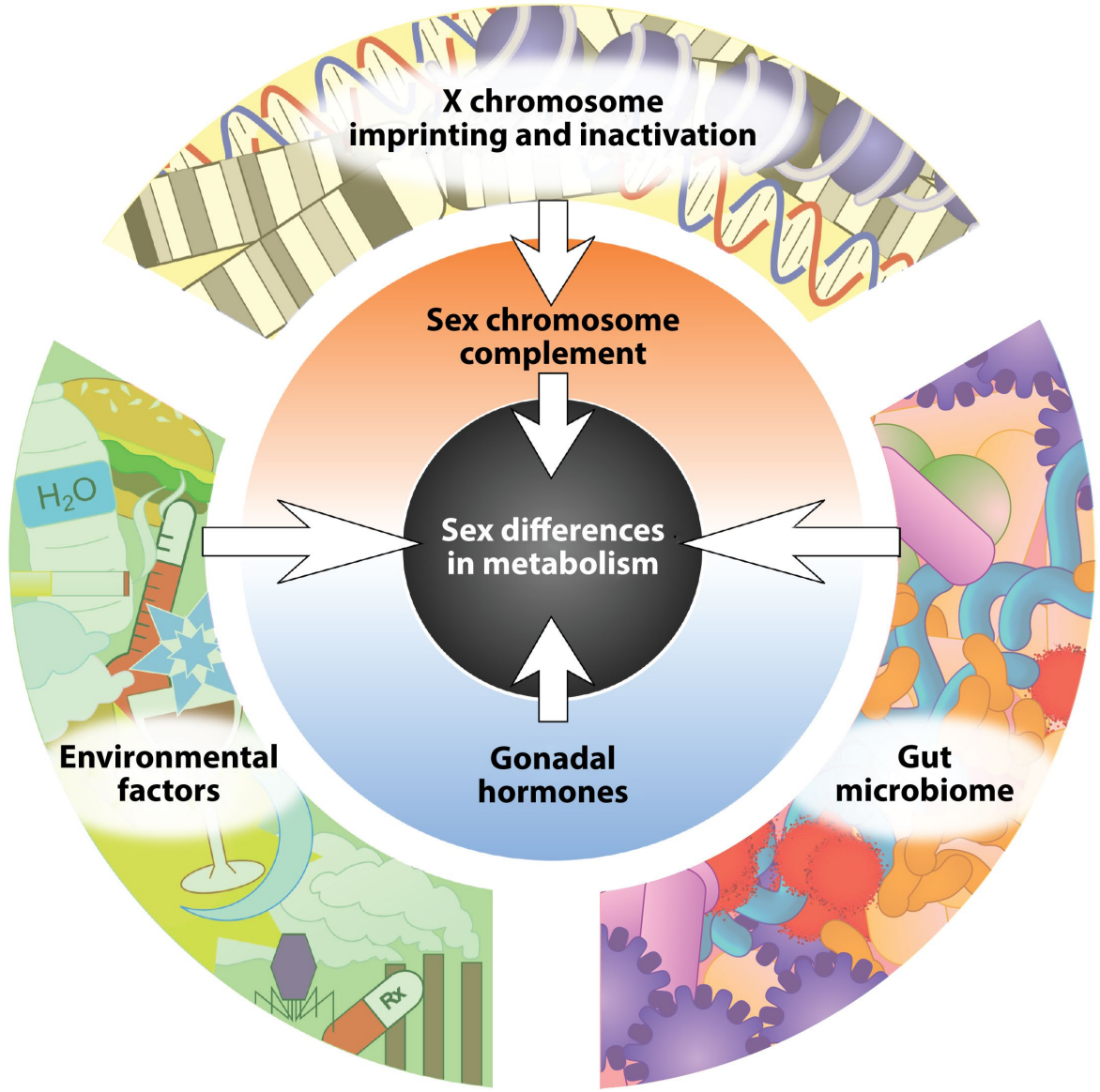


Source: Kerr P, et al, Frontiers in Neuroendocrinology. 2020;59:100858.

From: **Clinical Advances in Sex- and Gender-Informed Medicine to Improve the Health of All: A Review**

JAMA Intern Med. 2020;180(4):574-583. doi:10.1001/jamainternmed.2019





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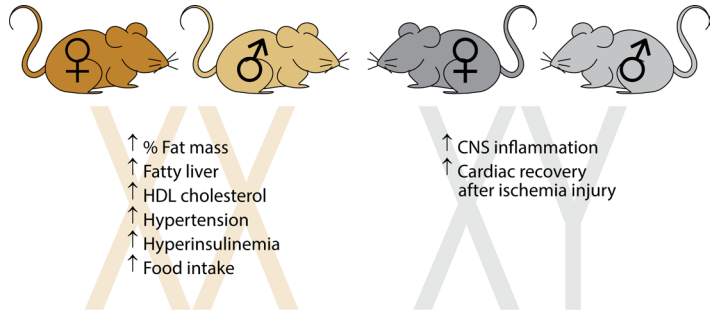

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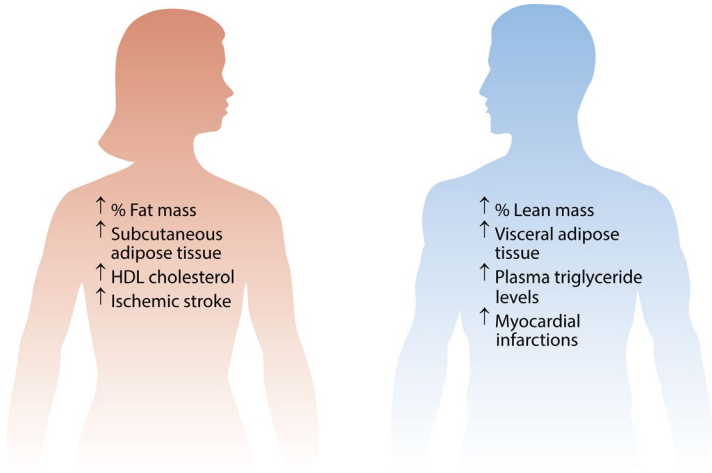

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Annu. Rev. Nutr. 37:225–45

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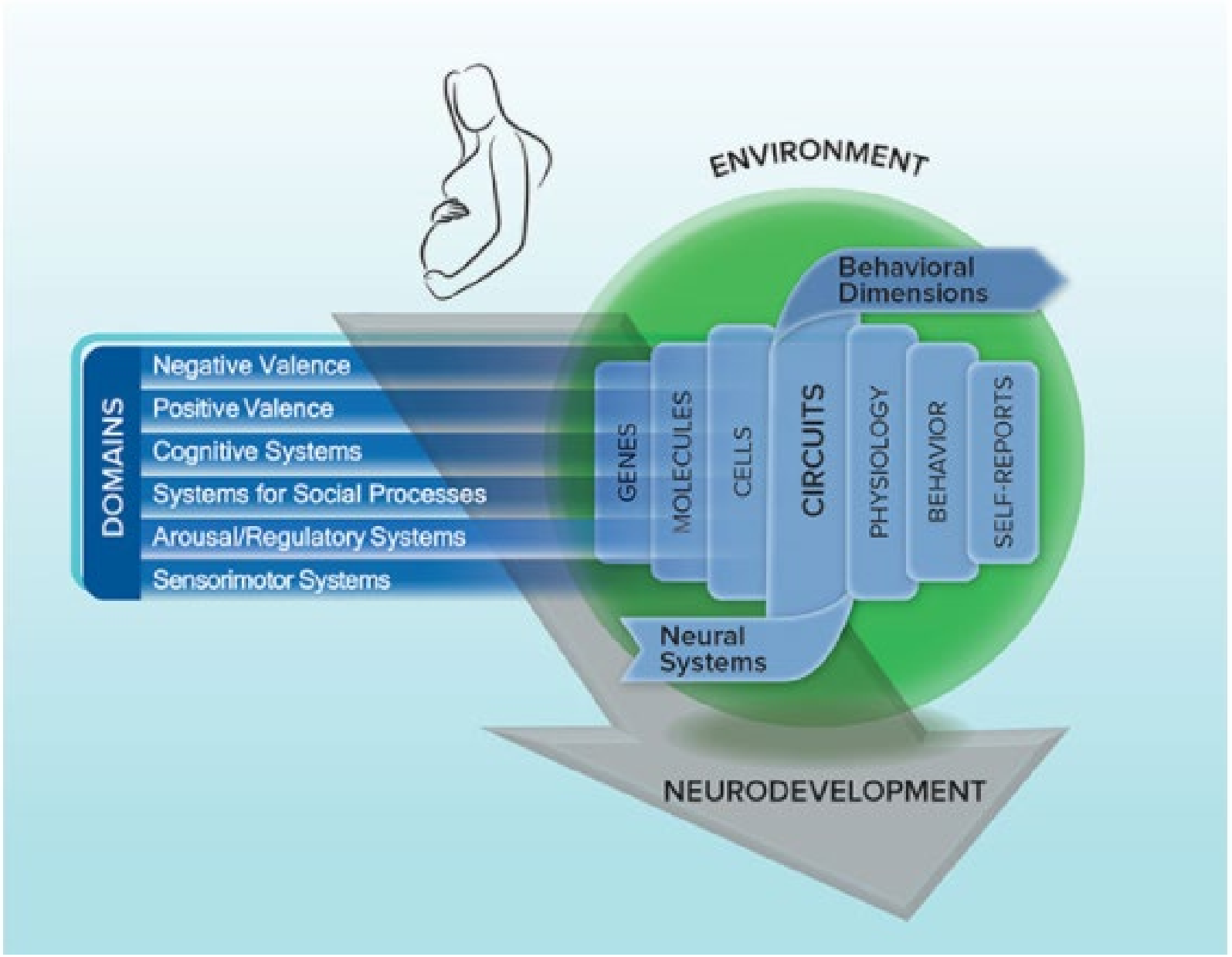
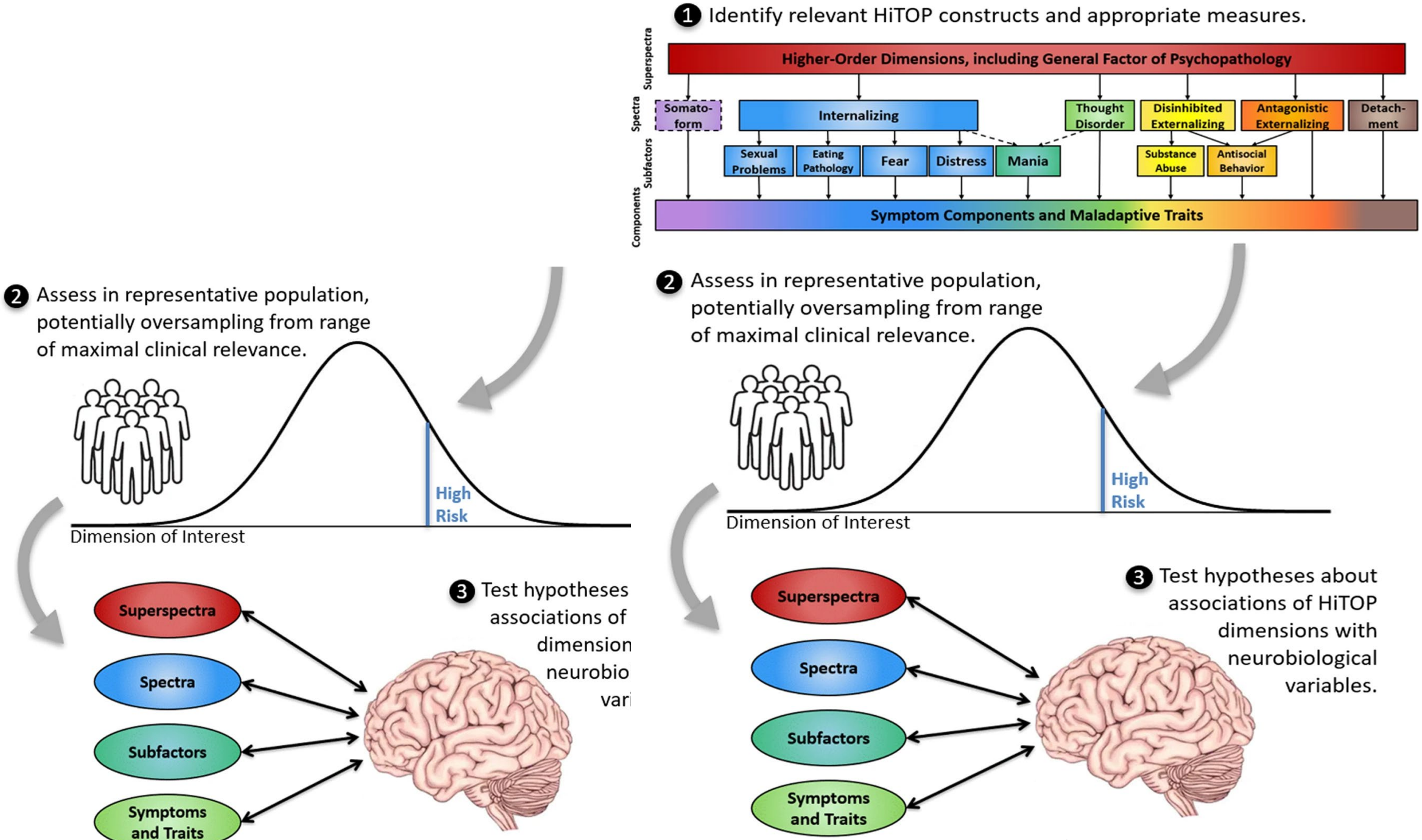
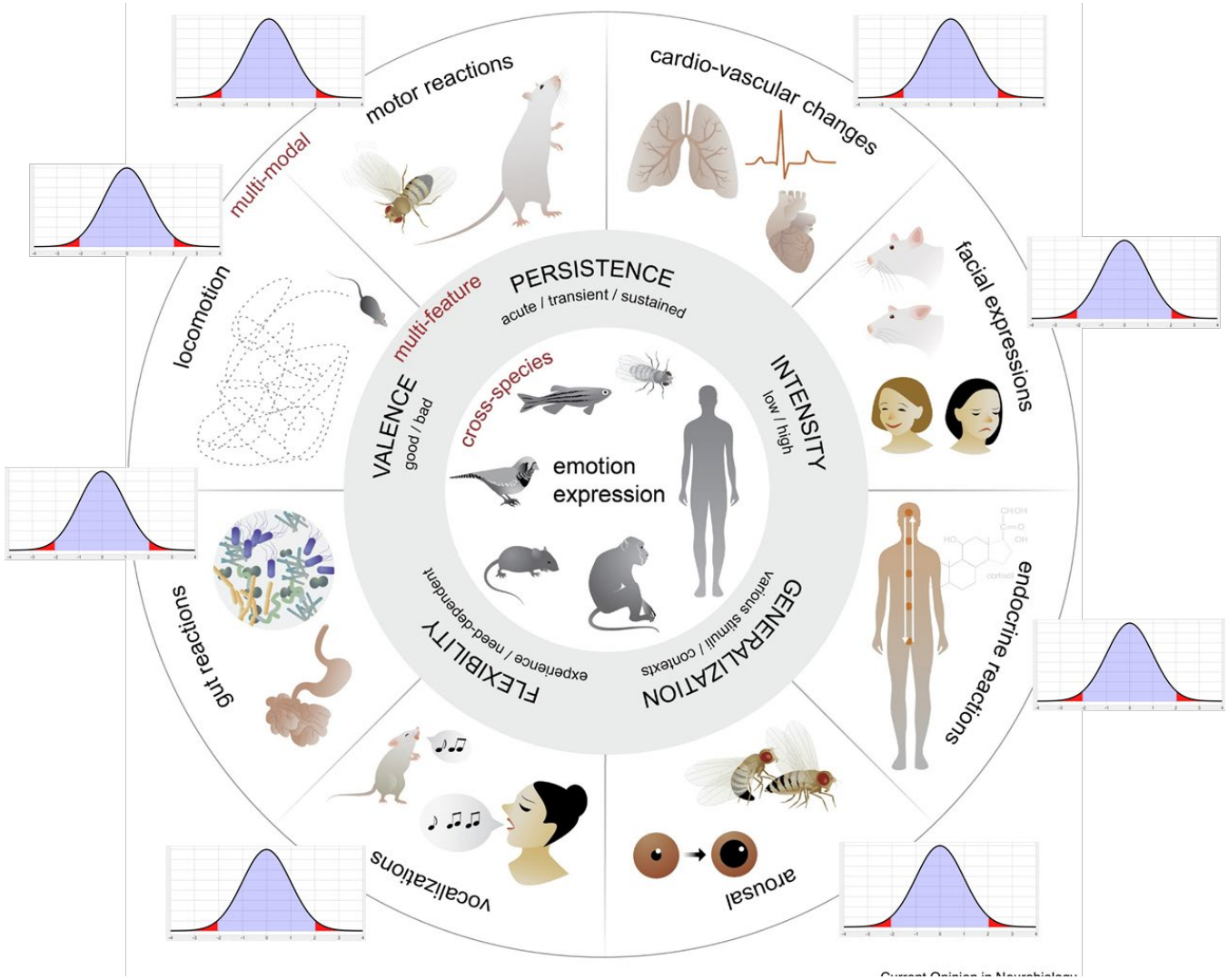
NIMH Research Domain Criteria (RDoC)



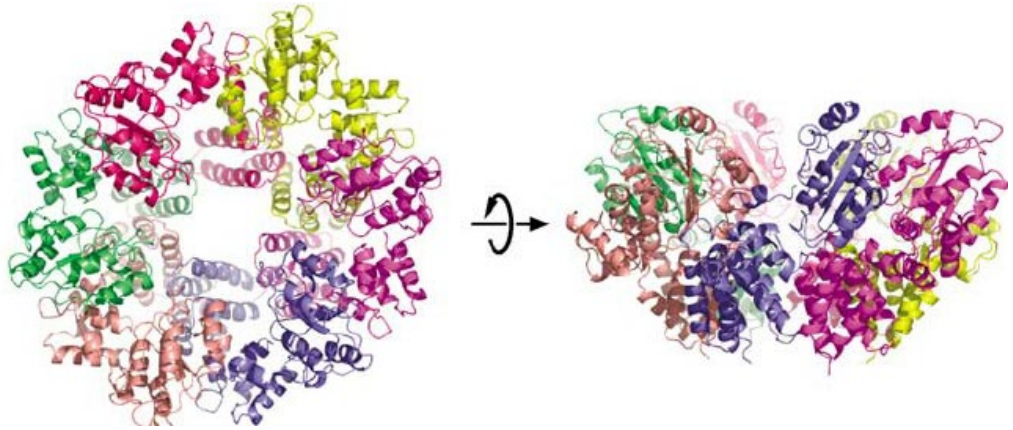


Latzman RD, DeYoung CG, Afzali MH, et al. *Neuropsychopharmacology. 2020*

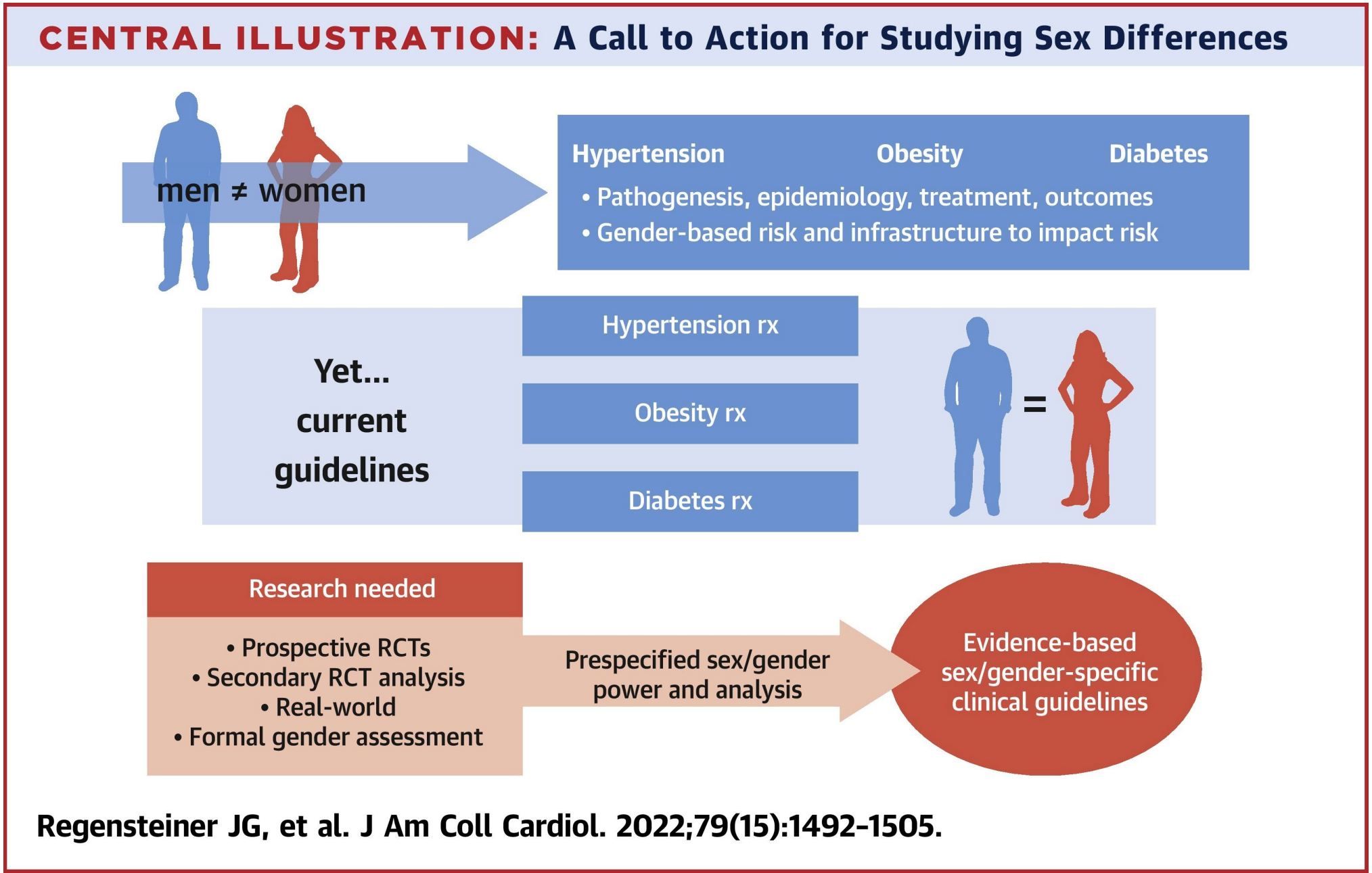
Computational Approaches to Understand Neuropsychopathology



Dynamic

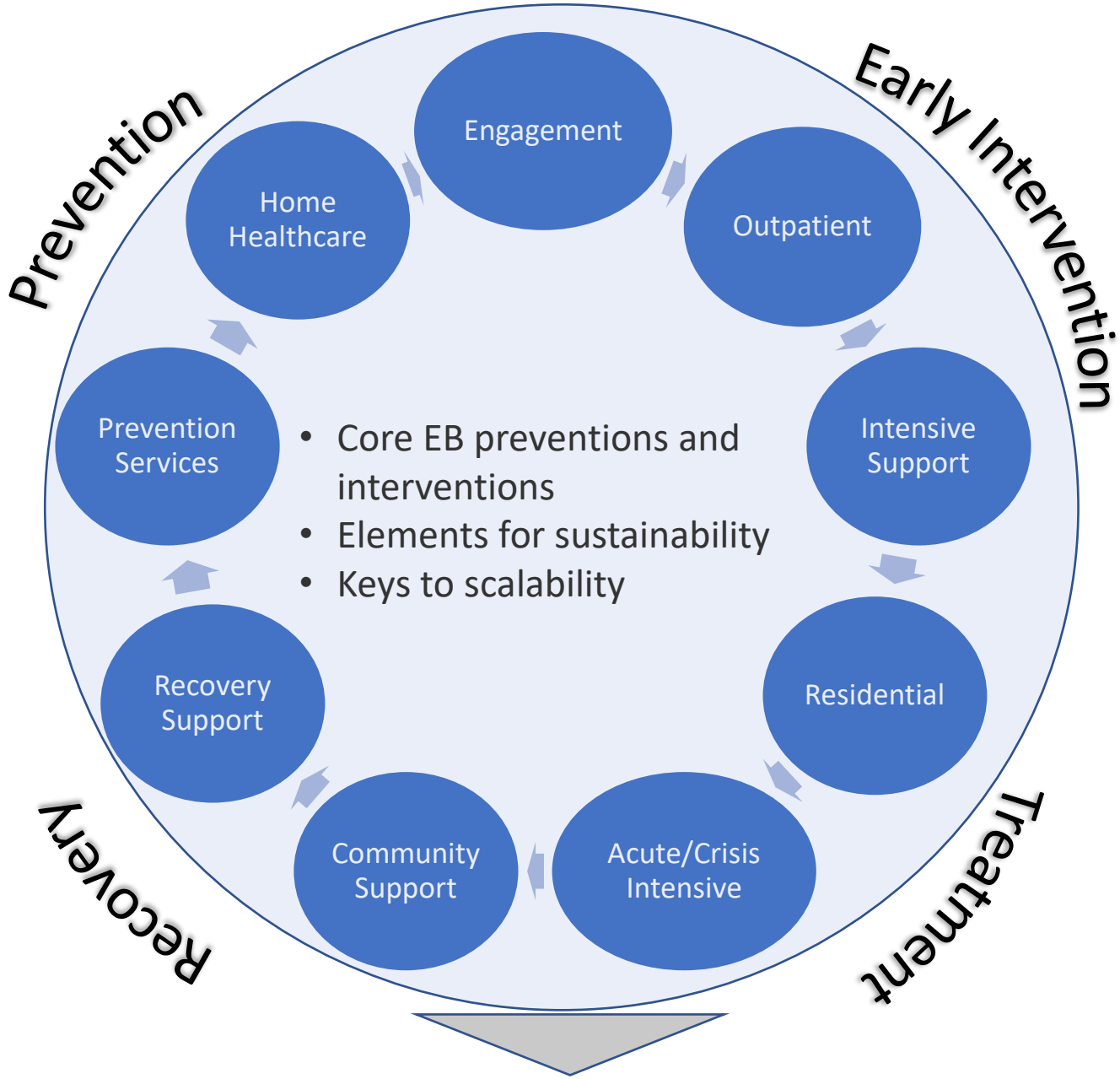


Evidence-based treatment without evidence



Regensteiner JG, et al. J Am Coll Cardiol. 2022;79(15):1492-1505.

Addressing morbidity in NIH-funded research: Implementation Research



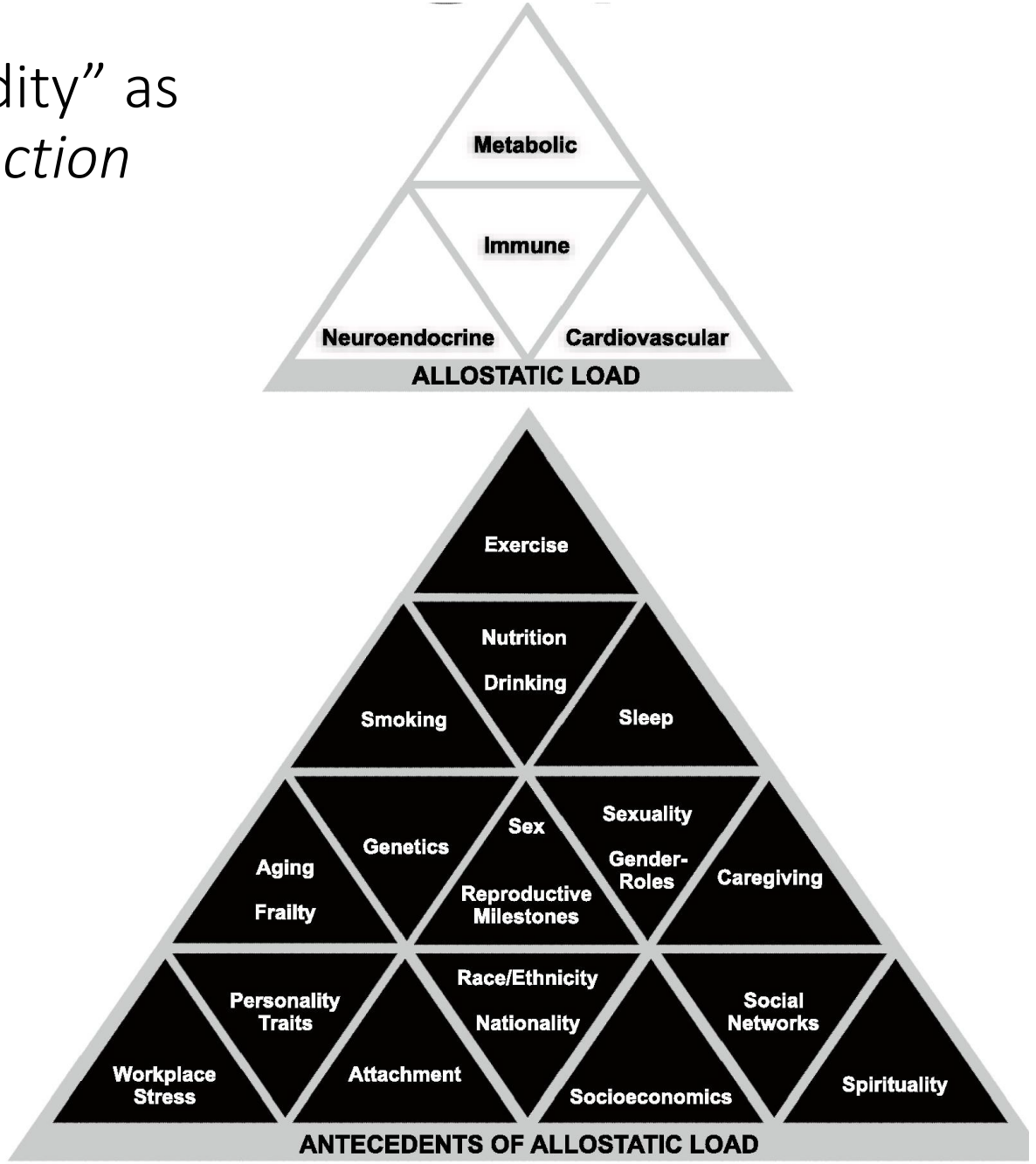
State and Local Health Agencies

Multidisciplinary teams Multidimensional data
Multi-level Research

Clinical Research
Clinicians/Health Records
Epidemiology
Cognitive and Data Sciences
Computational Sciences
Cognitive and System Neuroscience
Engineering / Gadget people
Ethologists and Evolutionary Biologists
Patient advocates/stakeholders

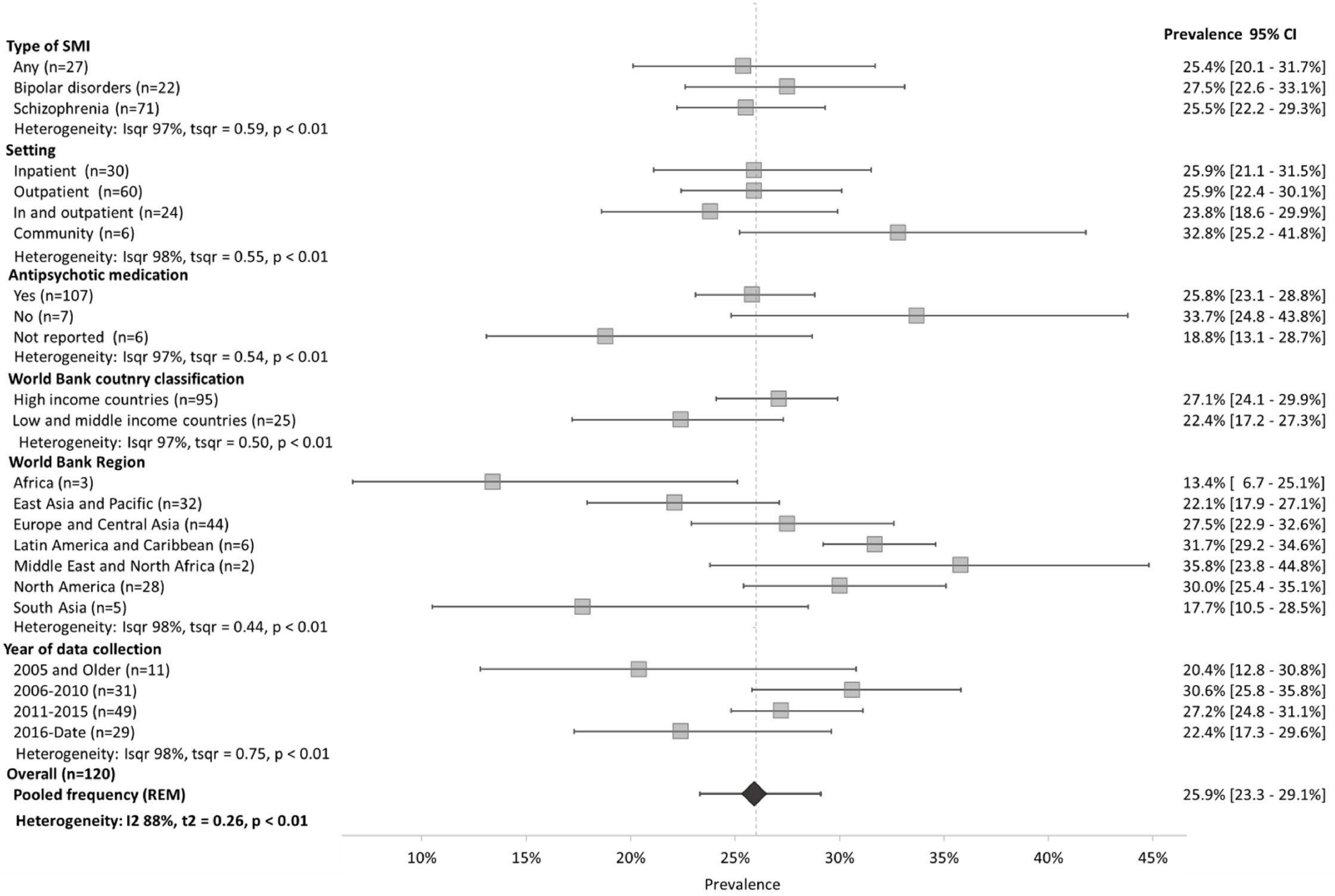
Translational research: Studying “morbidity” as deviations along *integrated systems function*

- Dimensions/Domains of function rather than the concept of diseases as discrete entities.
- Understanding how functional deviations in one system impact other systems



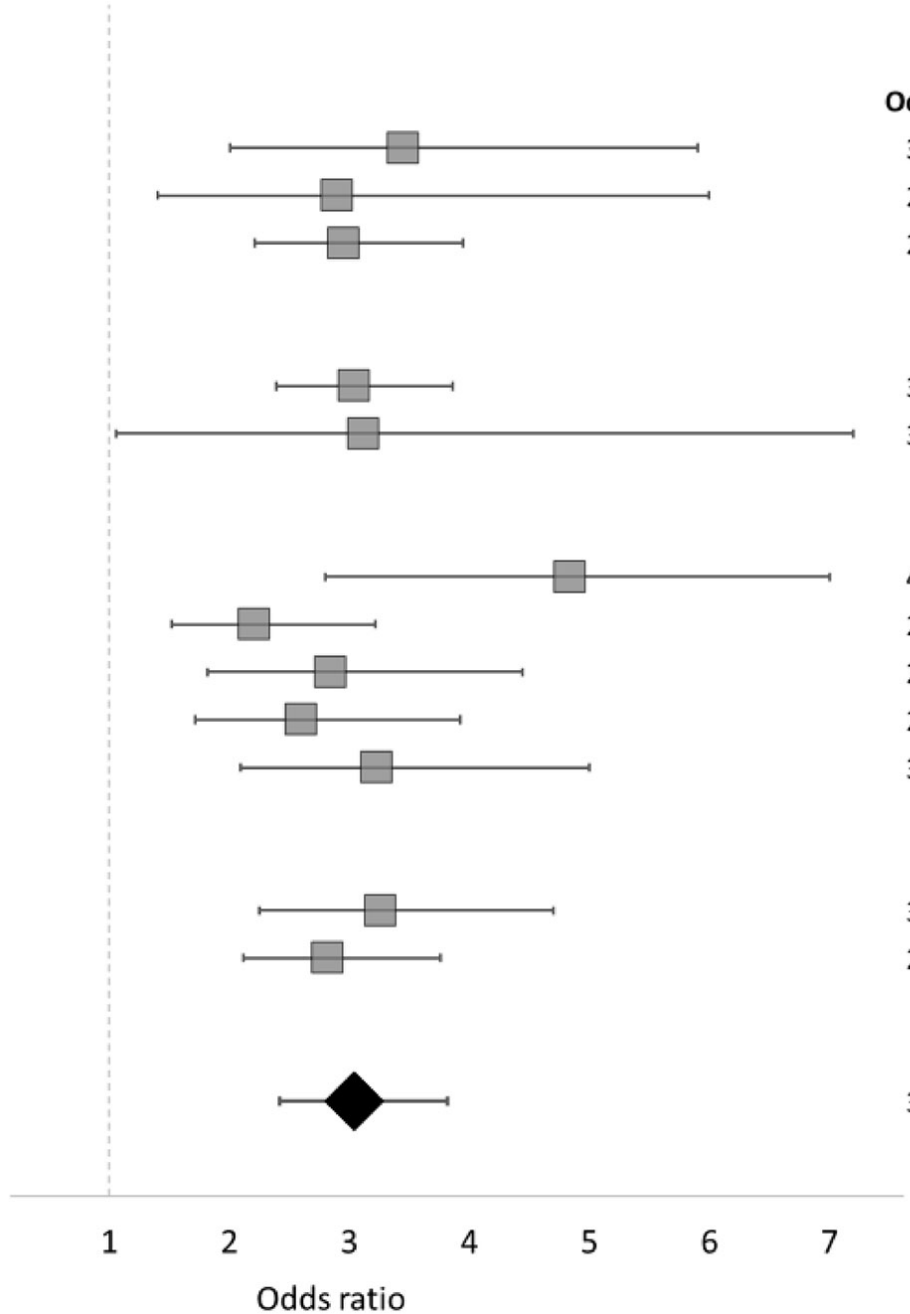
Source: Kerr P, et al, Frontiers in Neuroendocrinology. 2020;59:100858.

Prevalence of obesity in people with SMI

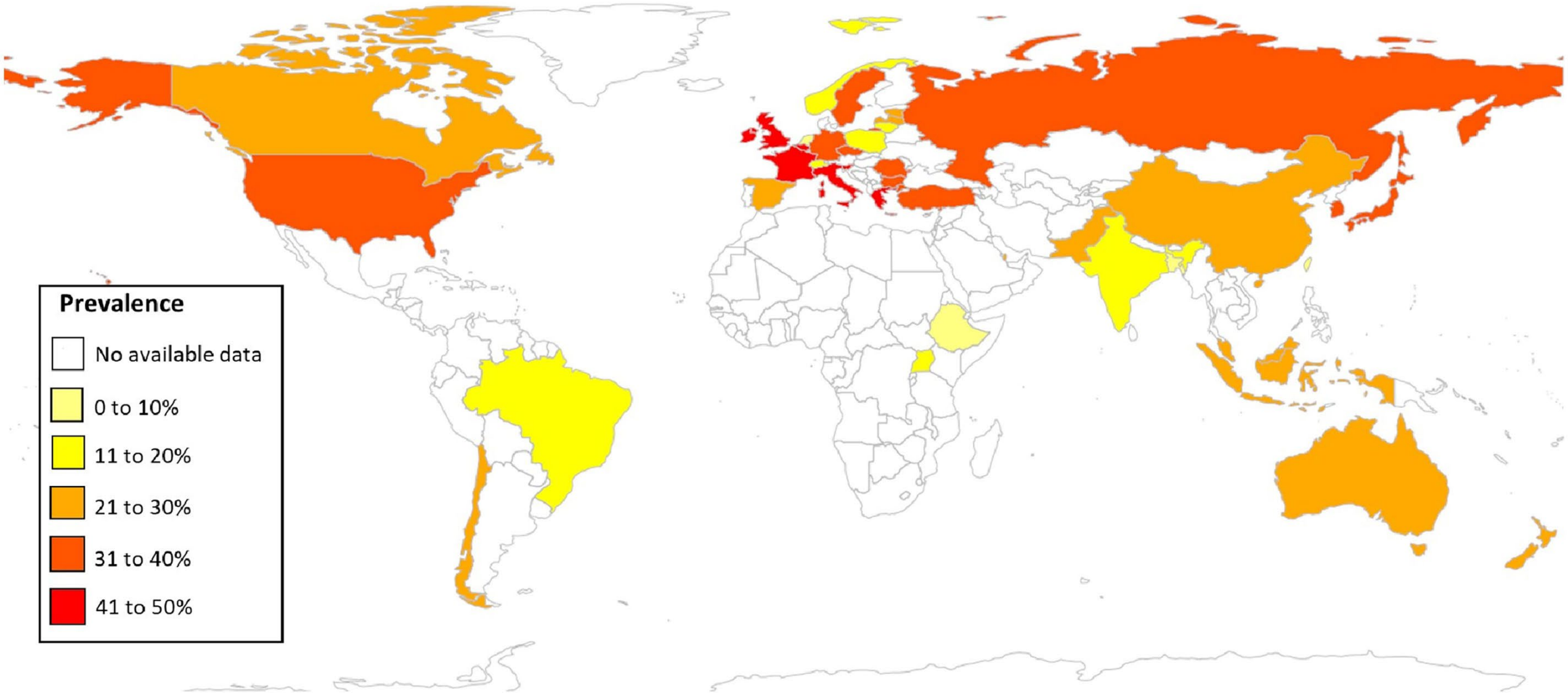


Odds of people with SMI of having obesity as compared with the general population

	People with SMI		General Population		
	Events	Total	Events	Total	Odds ratio 95% CI
Type of SMI					
Any (n=5)	370	1482	7479	51824	3.45 [2.01 - 5.90]
Bipolar disorders (n=3)	169	459	1640	5461	2.90 [1.40 - 6.00]
Schizophrenia (n=16)	1438	5225	3359	25748	2.95 [2.21 - 3.95]
Heterogeneity: Isqr 89%, tsqr = 0.28, p < 0.01					
World Bank coutnry classification					
High income countries (n=21)	1700	6173	12045	76501	3.04 [2.39 - 3.86]
Low and middle income countries (n=3)	267	992	423	6532	3.12 [1.06 - 7.20]
Heterogeneity: Isqr 93%, tsqr = 0.84, p < 0.01					
World Bank Region					
East Asia and Pacific (n=12)	945	3460	3248	39584	4.84 [2.80 - 7.00]
Europe and Central Asia (n=4)	409	2181	863	6805	2.21 [1.52 - 3.22]
Latin America and Caribbean (n=2)	53	173	83	589	2.84 [1.82 - 4.44]
Middle East and North Africa (n=1)	63	233	61	466	2.60 [1.72 - 3.92]
North America (n=5)	497	1118	8213	35589	3.23 [2.09 - 5.00]
Heterogeneity: Isqr 89%, tsqr = 0.21, p < 0.01					
Year of data collection					
2011 to Date (n=12)	1277	4875	2853	33772	3.26 [2.25 - 4.70]
Before 2010 (n=12)	690	2290	9615	49261	2.82 [2.12 - 3.76]
Heterogeneity: Isqr 88%, tsqr = 0.19, p < 0.01					
Overall					
Pooled OR (REM)		7165		83033	3.04 [2.42 - 3.82]
Heterogeneity: Isqr 88%, tsqr = 0.26, p < 0.01					

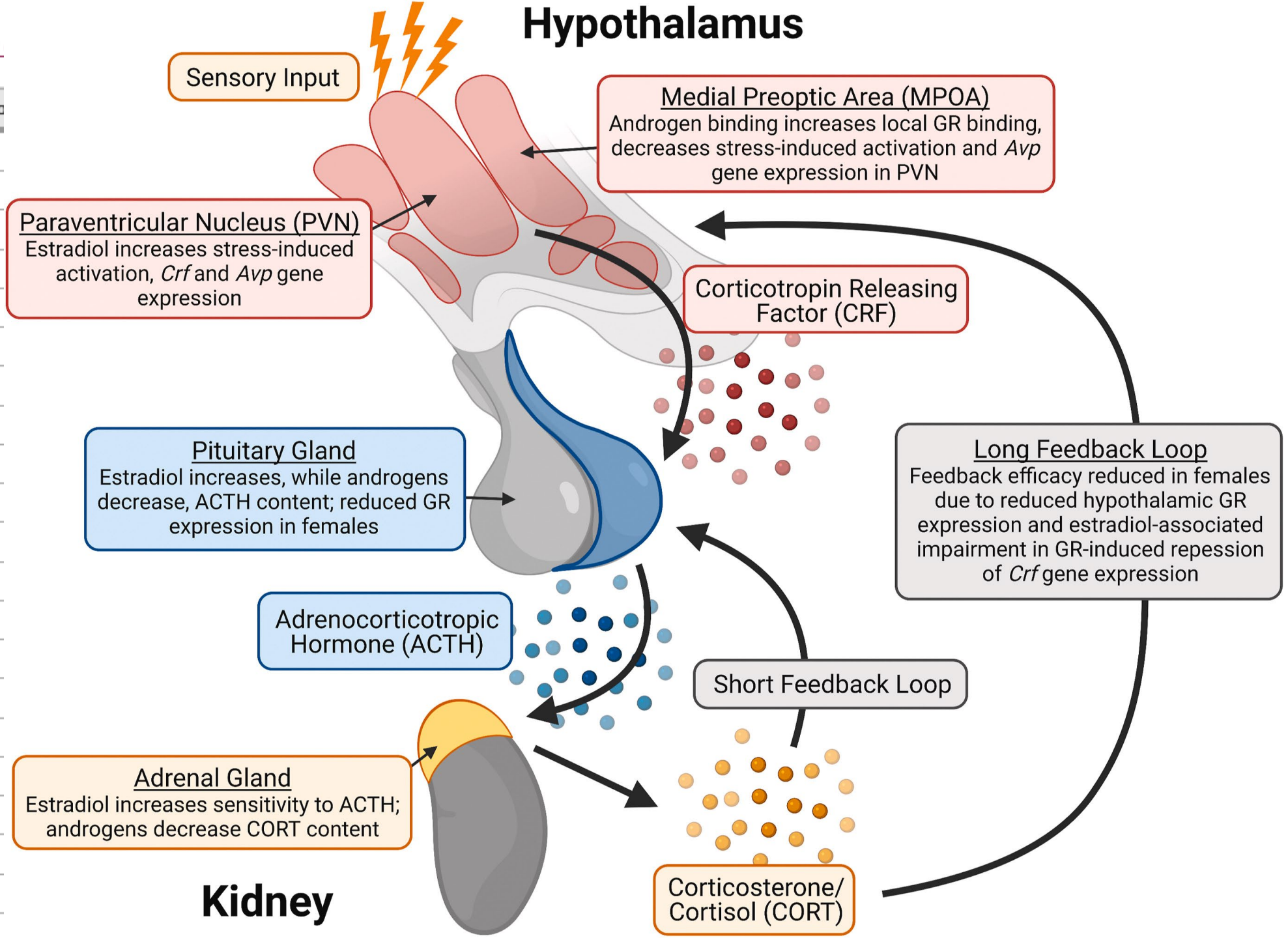


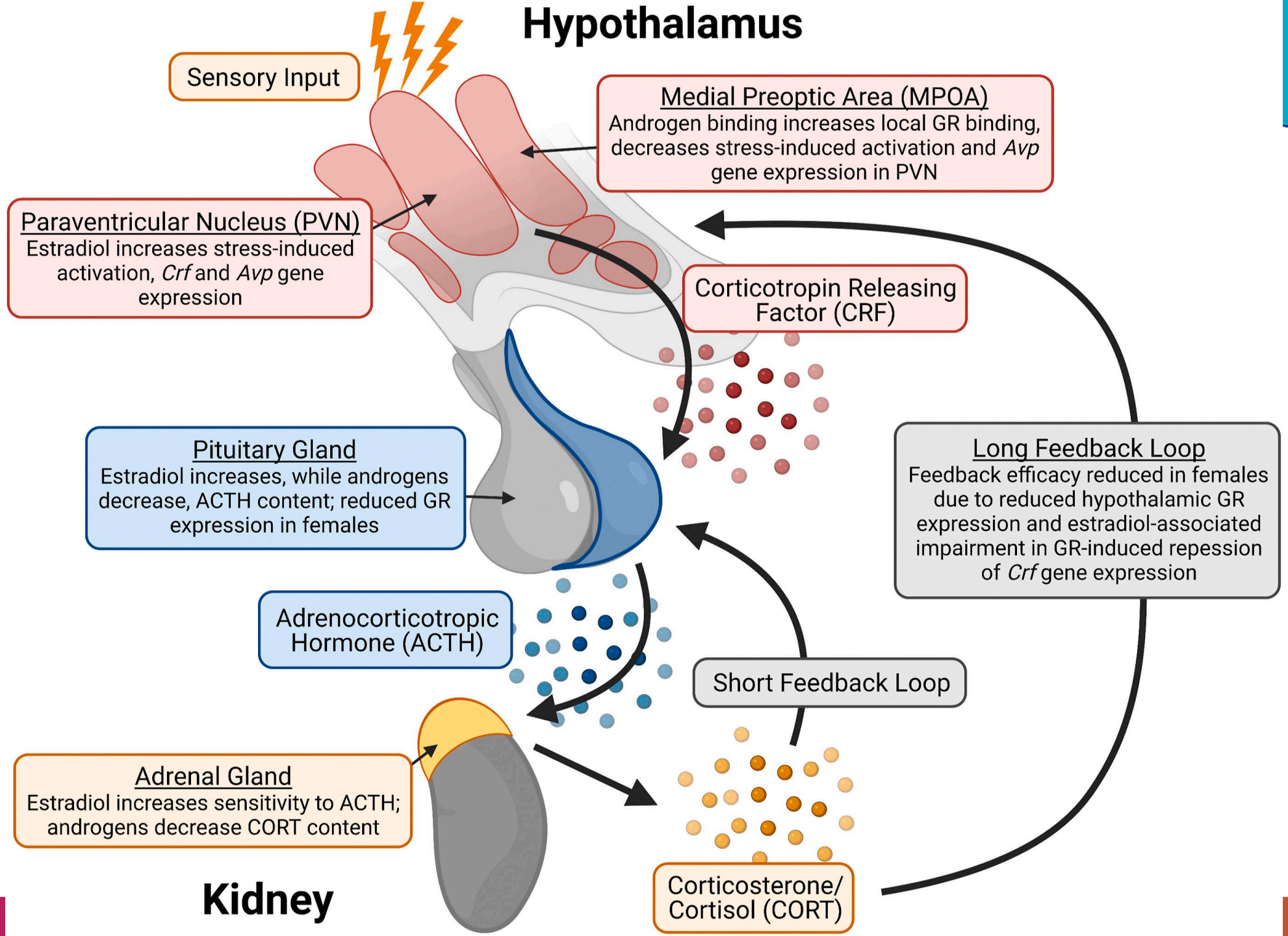
Prevalence of obesity in people with severe mental illness

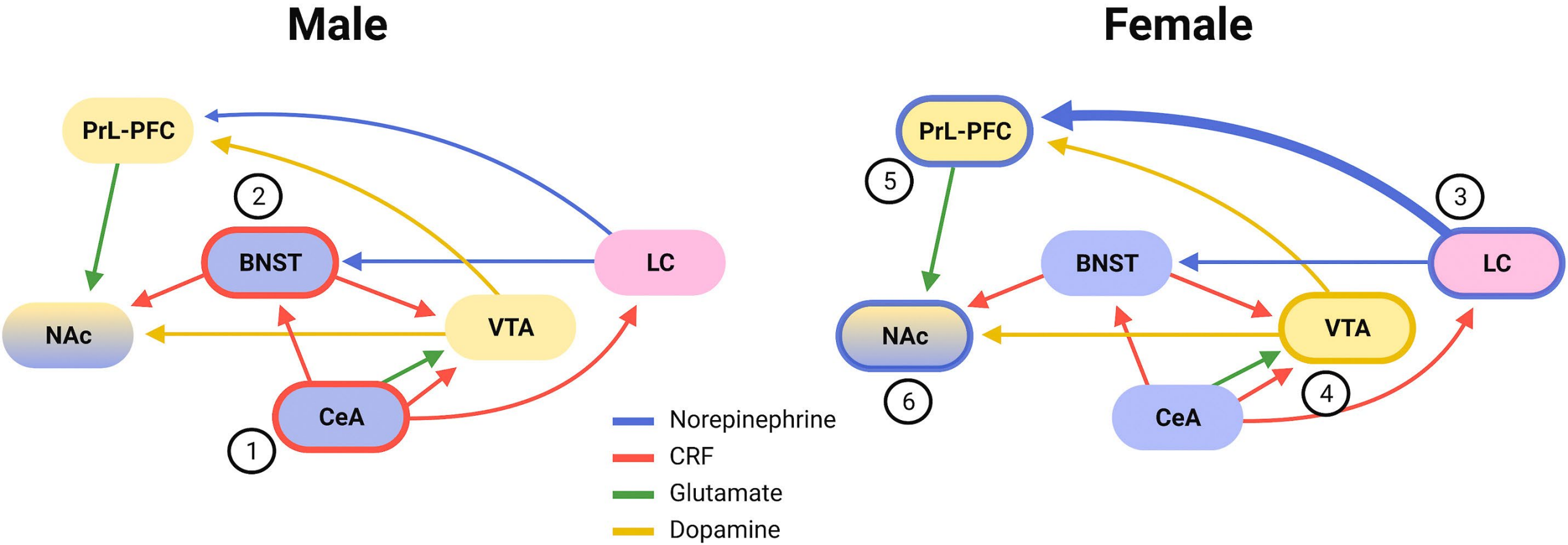


of sex and gender

	SABV inco
	No
	No
	No
	No
	No
	Yes
	No
	No
	No
	No
	No
	No
	No
	No
	No
	No
	No
	Yes




Hypothalamus
Sensory Input
Medial Preoptic Area (MPOA)
Androgen binding increases local GR binding, decreases stress-induced activation and *Avp* gene expression in PVN
Paraventricular Nucleus (PVN)
Estradiol increases stress-induced activation, *Crf* and *Avp* gene expression
Corticotropin Releasing Factor (CRF)
Pituitary Gland
Estradiol increases, while androgens decrease, ACTH content; reduced GR expression in females
Long Feedback Loop
Feedback efficacy reduced in females due to reduced hypothalamic GR expression and estradiol-associated impairment in GR-induced repession of *Crf* gene expression
Adrenocorticotropic Hormone (ACTH)
Short Feedback Loop
Adrenal Gland
Estradiol increases sensitivity to ACTH; androgens decrease CORT content
Kidney
Corticosterone/ Cortisol (CORT)


Male
PrL-PFC
2
BNST
LC
NAc
VTA
CeA
1
Norepinephrine
CRF
Glutamate
Dopamine
Female
PrL-PFC
5
3
BNST
LC
NAc
VTA
6
4
CeA

Landscape Analysis of Research on Multimorbidity
An example from NIDA

Chronic conditions progress to multimorbidity

NIDA's ORWH Portfolio Analysis Team

Rita Valentino, *Division Director, DNB*

Susan Wright, *Program Officer, DNB*

Christie Espinoza, *Program Analyst, DNB*

Keisher Highsmith, *Program Officer, DESPR*

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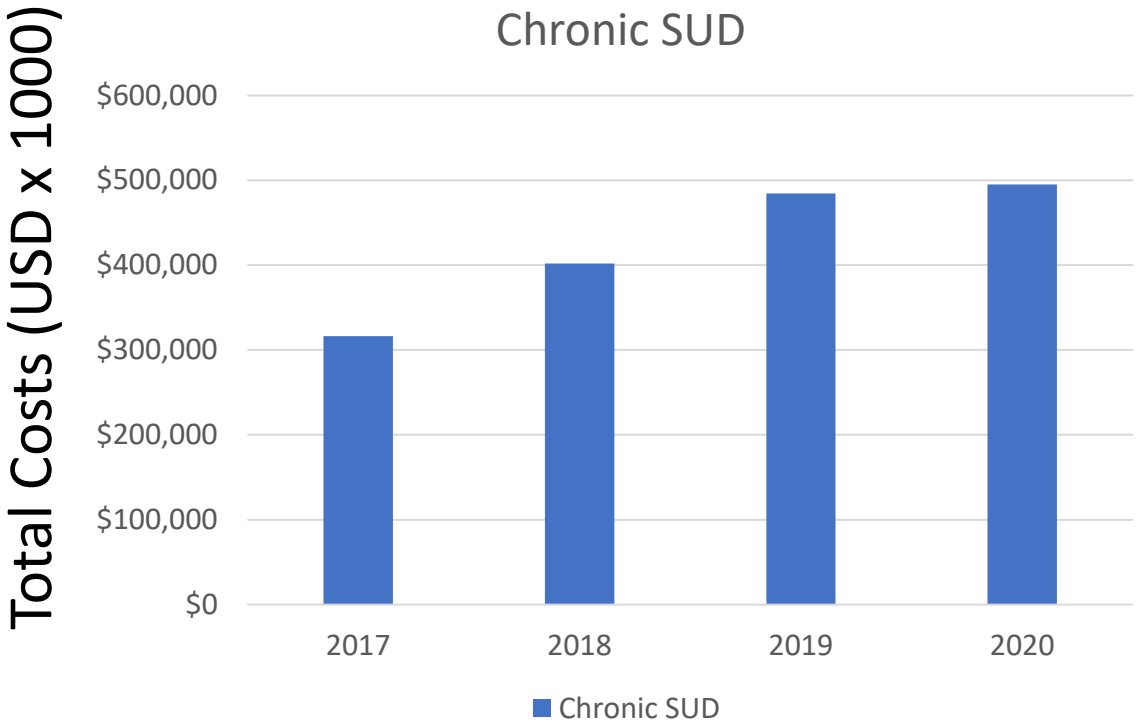
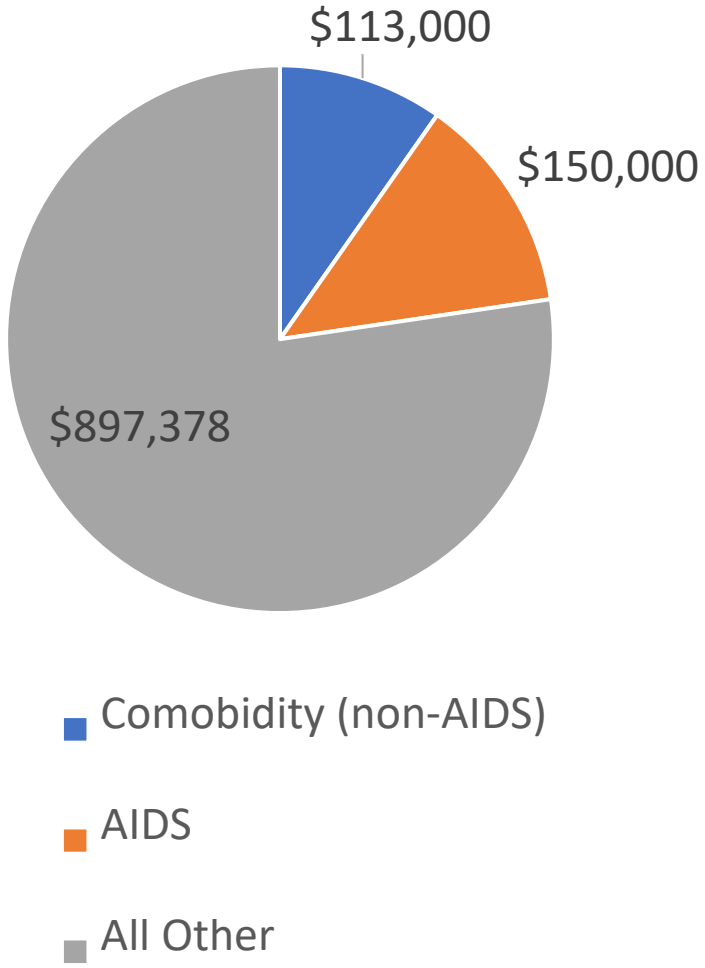
Substance Use Disorder as a Chronic Debilitating Condition



Commitment to Research on Multimorbidities ($ x 1000)



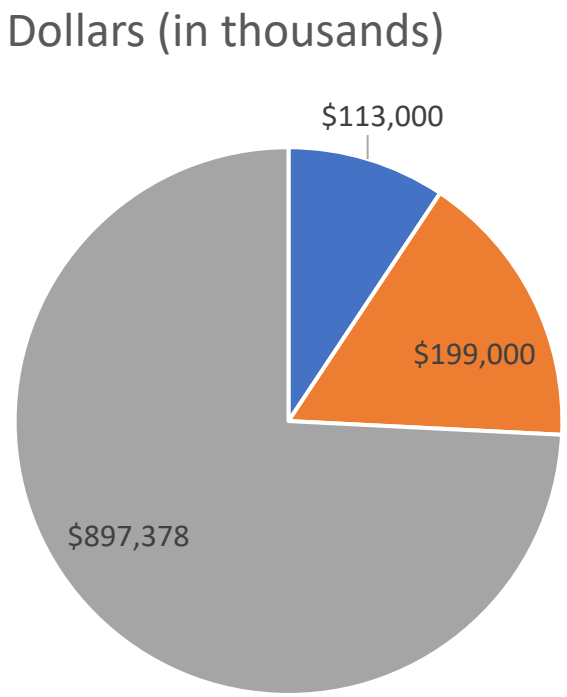
Next step in analysis:

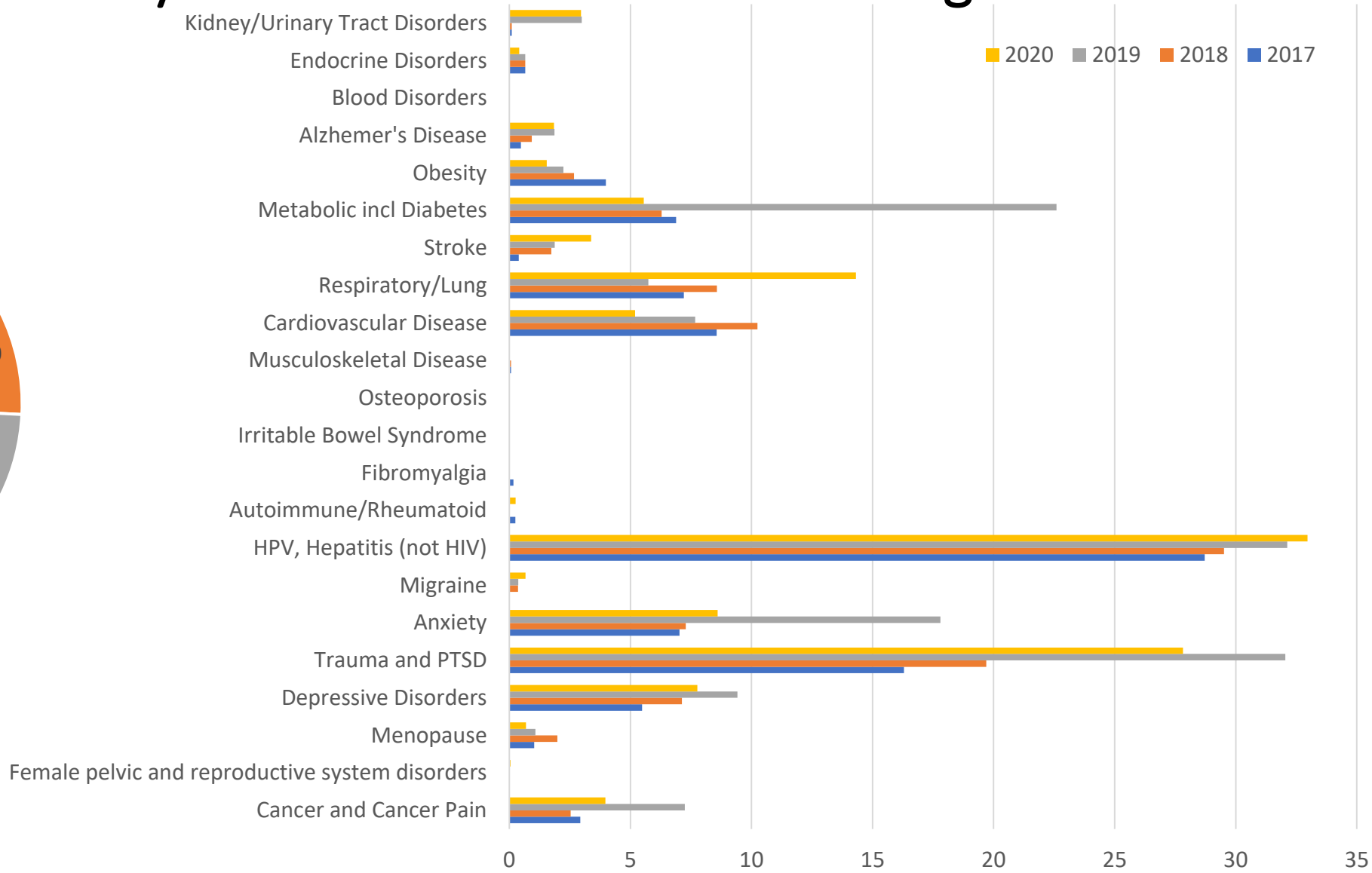
Substance Use Disorder X

Category	Condition (2019 DALY)								
Female Specific	Cancers of the female reproductive tract* (900,843)	Dys-menorrhea/ Menstrual Abnormalities (289,608)	Fibroids* (64,009)	Endometriosis* and Adenomyosis (53,777)	Infertility*/ Early Pregnancy Loss (26,355)	Polycystic Ovarian Syndrome (42,738)	Pelvic floor disorders, Organ prolapse (21,613)	Menopausal symptoms Pelvic Inflammatory Disease* Vulvodynia/Chronic gynecologic pain disorders – pelvic and vulvar Vaginosis	
More Common in Women/ Higher Morbidity for women	Depressive Disorders (1,704,524)	Migraine/ Headache (1,573,325)	Breast cancer* (1,387,670)	Sexually transmitted infections (37,316)	Rheumatoid Arthritis* (187,902)	Autoimmune diseases (*including RA) •SLE* •Sjögren's Syndrome* •Scleroderma*	Temporomandibular Muscle/Joint Disorder (TMJD) Chronic Fatigue Syndrome* Fibromyalgia* Candidiasis Post-traumatic stress Irritable Bowel syndrome HPV infection Osteoporosis		
High morbidity for women	Musculo-skeletal disorders (8,170,164)	Cardio-vascular Disease (7,538,622)	Mental Health (4,164,912)	Chronic respiratory diseases (3,643,271)	Substance Use Disorders (2,736,126)	Stroke (2,098,900)	Diabetes (2,010,853)	Chronic Kidney Disease (1,105,286)	Obesity/metabolic disease Comorbidity with aging
higher morbidity/ potentially neglected in women	Unintentional Injuries (including intimate partner violence*) (2,050,026)	Alzheimers/ Dementia* (1,296,376)	Osteo-arthritis (1,257,042)	Endocrine, metabolic, blood, and immune disorders (853,247)	Recurrent UTI/ Interstitial Nephritis (201,529)	Multiple Sclerosis (143,123)	HIV (118,596)	Contraception- Exogenous hormone use- Neuropathy Overactive bladder/Incontinence Chronic pain including chronic pelvic pain	

*Per MCS-WH reporting guidance, the following RCDC disease categories are particularly relevant to women's health

SUD Comorbidity with other Chronic Debilitating Conditions





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