Obesity: The Intersection of Biology, Behavior, and Public Health

Abdul Badi Abou-Samra
Director, Qatar Metabolic Institute
Co-Chair, National Diabetes Committee
Chair, National Obesity Taskforce
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Disclosure Statement

Speaker:

Dr. Abdul Badi Abou Samra

- Has no relevant financial/non-financial relationships to disclose.
- Will not be discussing unlabeled/unapproved use of drugs or products.

Obesity: The Intersection of Biology, Behavior, and Public Health

Objectives:

To understand the interaction of

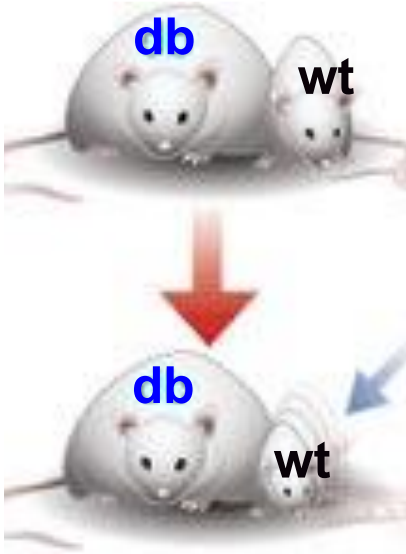
1. **Biology of weight maintenance**
2. **Behavior & body weight**
3. **Public Health & obesity**

1. Biology of weight maintenance - LEPTIN

The ob/ob mouse and db/db mouse are obese and diabetic:

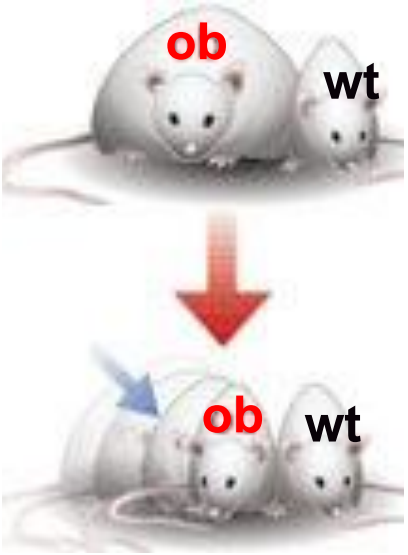
- Parabiosis of db/db & WT mice → the WT mouse stops eating and dies from cachexia (***Coleman DL and Hummel KP, AJP 1969***)

"Supra-physiologic levels of a soluble factor in the db/db causes cachexia of WT, the db/db mouse is resistant to it (LepR mutation)"



- Parabiosis of ob/ob & WT mice cures obesity of the ob/ob mouse (***Coleman DL, Acta Endocr. 1973***)

"**a soluble factor from the WT mouse cures obesity of the ob/ob mouse; ob/ob mouse is deficient in this factor (Leptin mutation)!**".

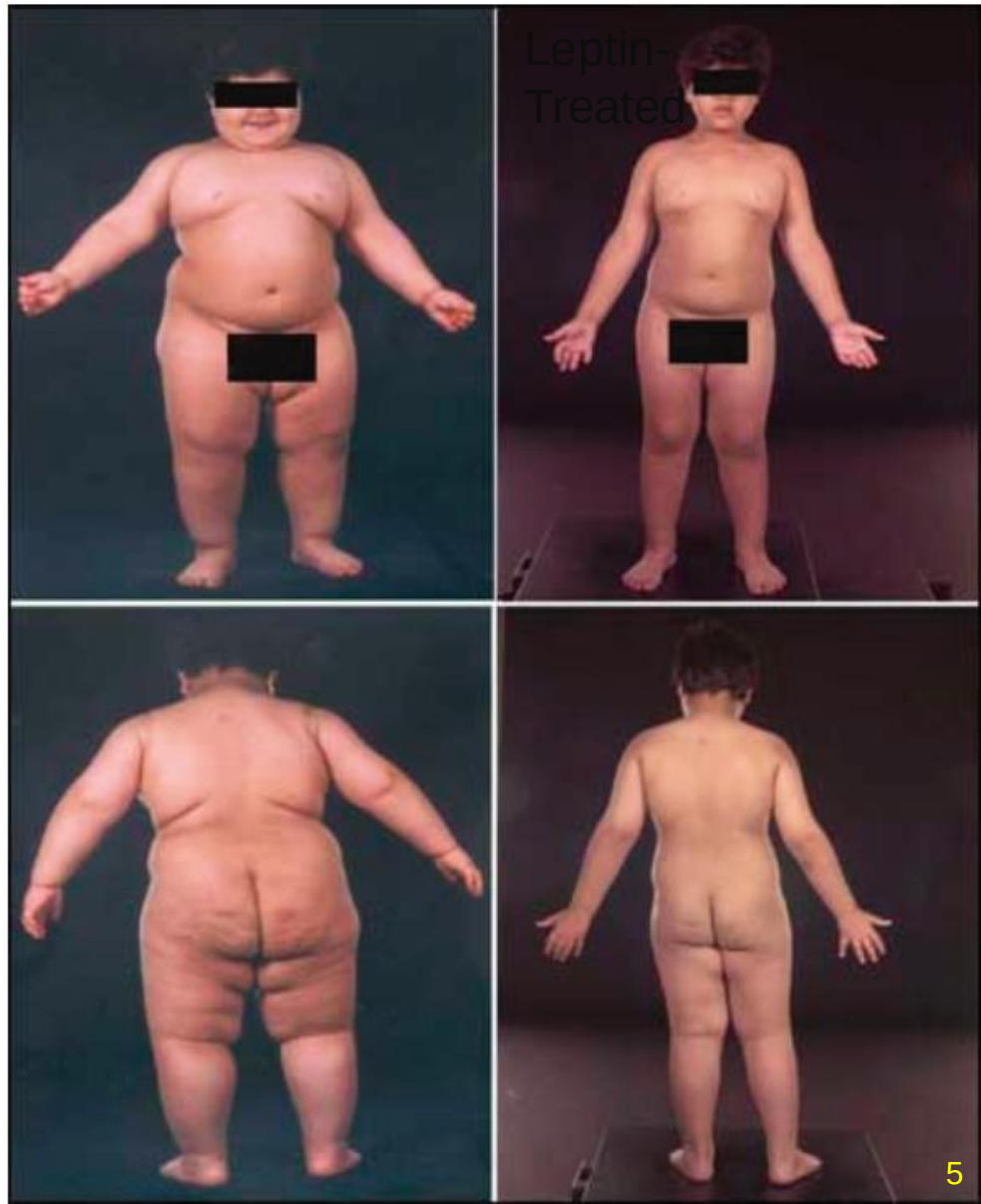


1. Biology of weight maintenance - LEPTIN

Leptin Deficiency Syndrome

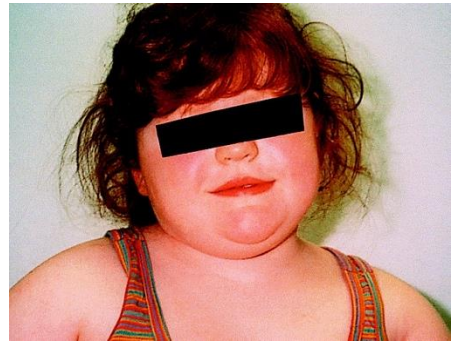
Farooqi et al. NEJM 1999

- Leptin mutation discovered in a family with severe obesity and diabetes – similar features to ob/ob mouse!
- Leptin deficiency can be treated by leptin
- **Patients with obesity have resistance to leptin. Their leptin levels are high. Leptin is not useful to treat common obesity.**



1. Biology of weight maintenance - αMSH

- Agouti mouse is obese and golden color
  - Ectopic expression of "Agouti Signaling Protein (ASIP/AgRP) (αMSH antagonist).
  - **ASIP/AgRP antagonizes αMSH at MC4 receptor in the hypothalamus ⇒ Obesity.**
  - **ASIP/AgRP antagonizes αMSH at MC1 receptor in melanocytes ⇒ yellow color.**



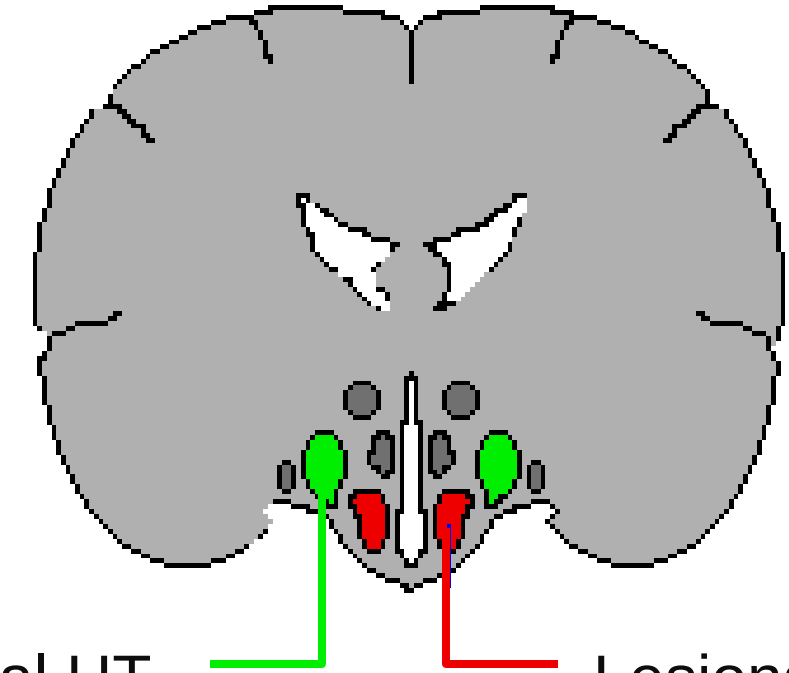
- POMC Deficiency in human: hyperphagia and obesity (deficiency of MSH MC4), red hair (deficiency of MSH, MC1) and Neonatal adrenal insufficiency (deficiency of ACTH).
- **MCR4 mutation in human → obesity only**
- **AgRP mutation (A67T) in human → resistant to obesity (high BMR)**

1. Biology of weight maintenance – animal physiology

Response to Starvation and Forced Feeding

1. Biology of weight maintenance – animal physiology

Hypothetical Hunger and Satiety Centers in Rodents Are Experimentally Defined

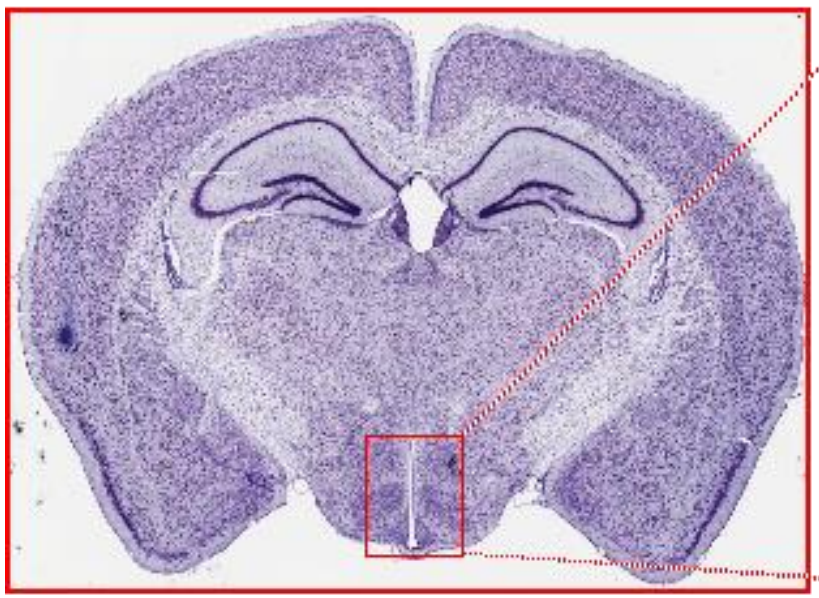


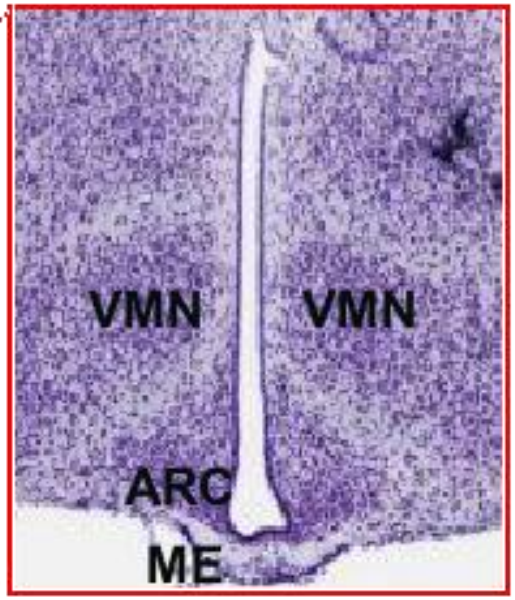
Lesions in Lateral HT lead to anorexia and weight loss (hunger center)

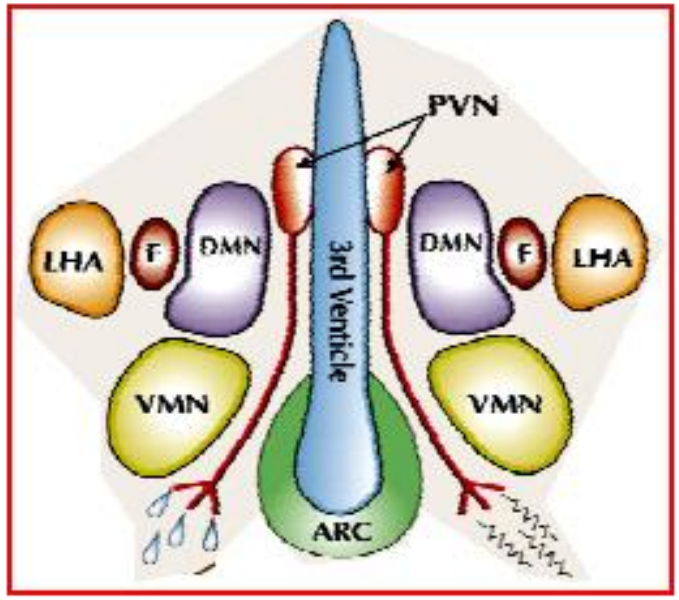
Lesions in Ventromedial HT lead to overeating and obesity (satiety center)

1. Biology of weight maintenance – animal physiology

Neuro-circuits within the Arcuate Nucleus and nearby nuclei regulate food intake!!!!!!!





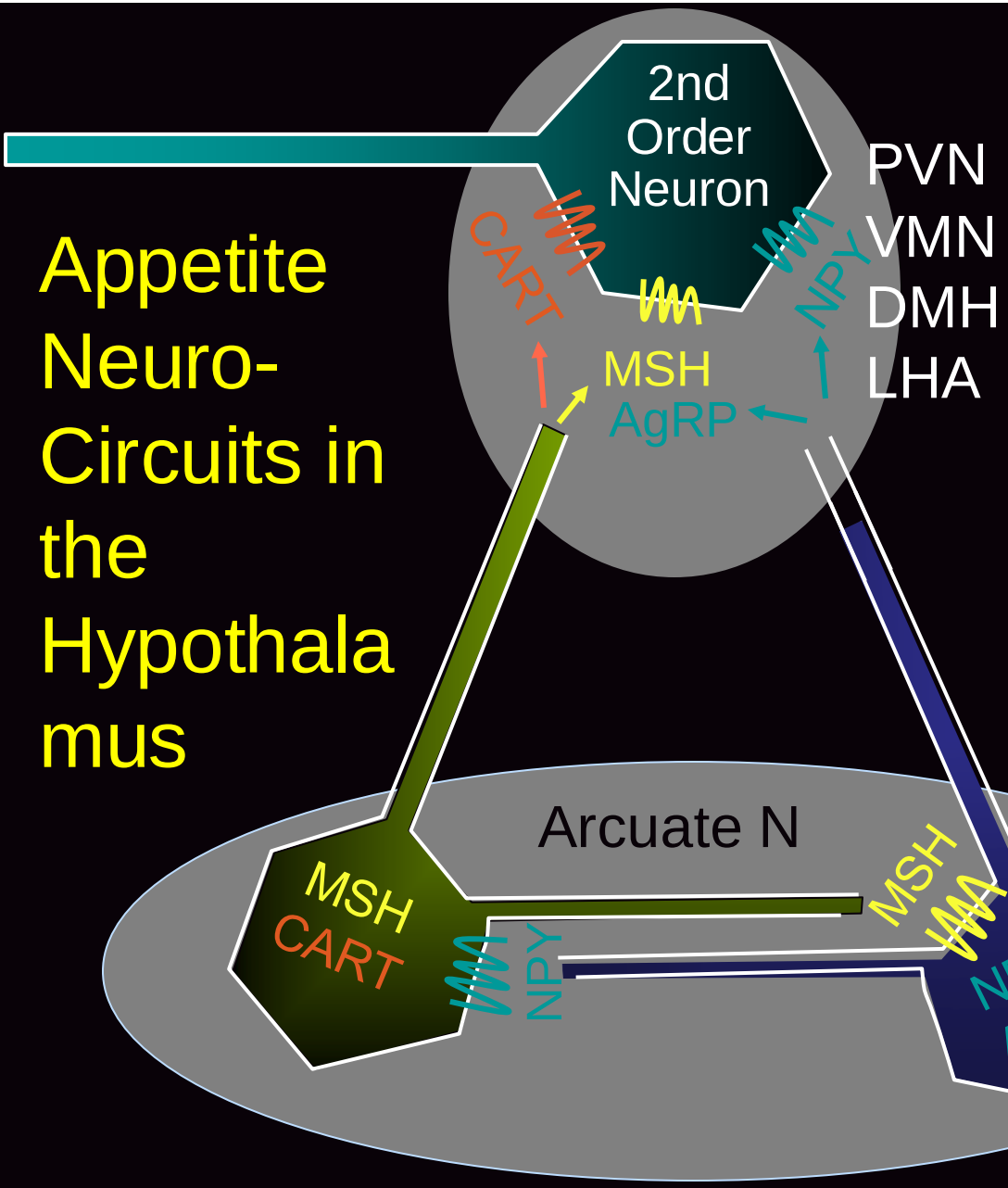


ARCUATE NUCLEUS

- Neurons co-express NPY/AgRP: increase feeding
- Neurons co-express αMSH/CART*: suppress feeding

*CART: cocaine- and amphetamine-regulated transcript

1. Biology of weight maintenance – animal physiology



2nd Order Neurons
PVN: TRH, CRH
VMN: BDNF
DMH: NPY
LHA/Fornix: MCH, Orexins

1st Order Neurons in the Arcuate N:
MSH/CART ⇓ Feeding
NPY/AgRP ⇑ Feeding

1. Biology of weight maintenance – animal physiology

Appetite Neuro-Circuits in the Hypothalamus

2nd Order Neuron

PVN
VMN
DMH
LHA

CART
MSH
AgRP
NPY

Arcuate N

MSH
CART
NPY

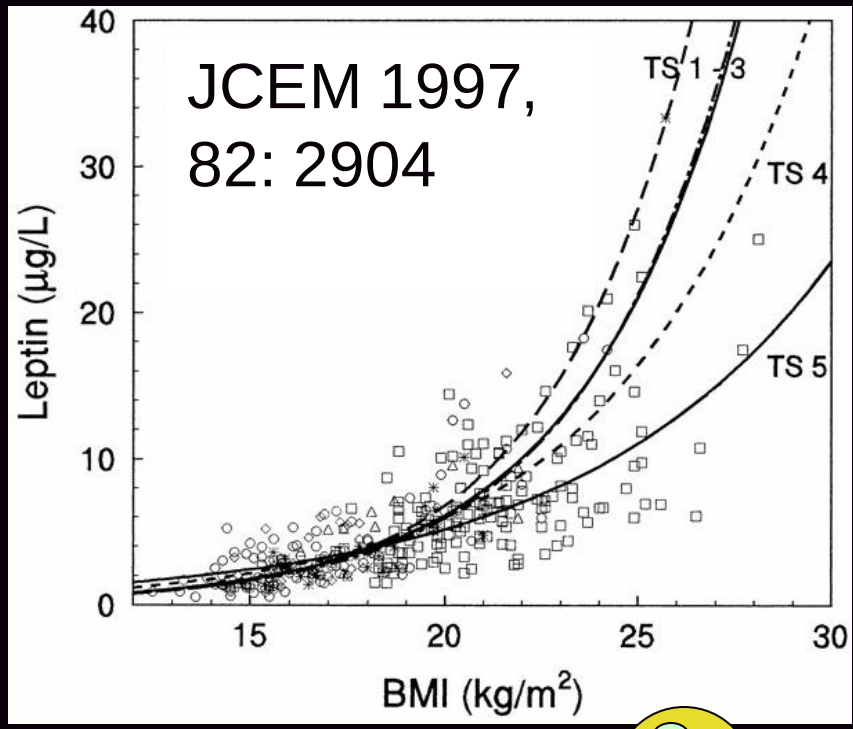
MSH
NPY
AgRP

LepR
+

LepR
−

Leptin

Leptin Resistance in Obesity



1. Biology of weight maintenance – our genes?

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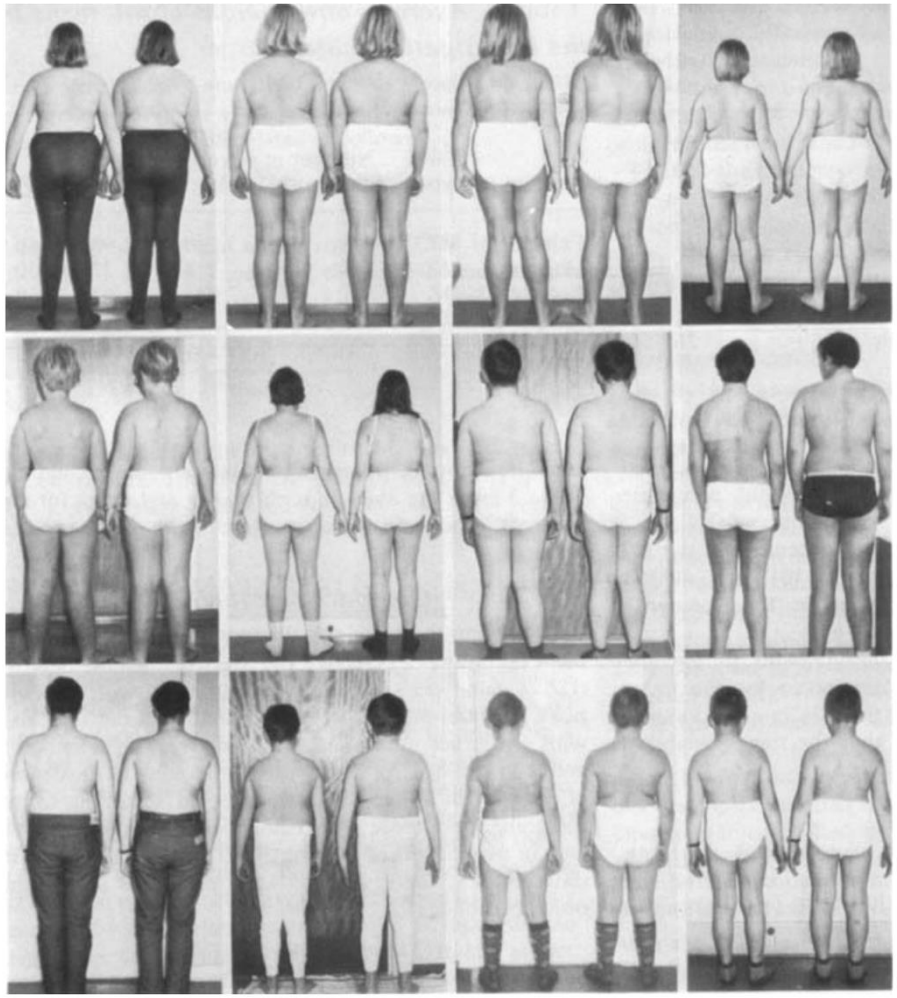
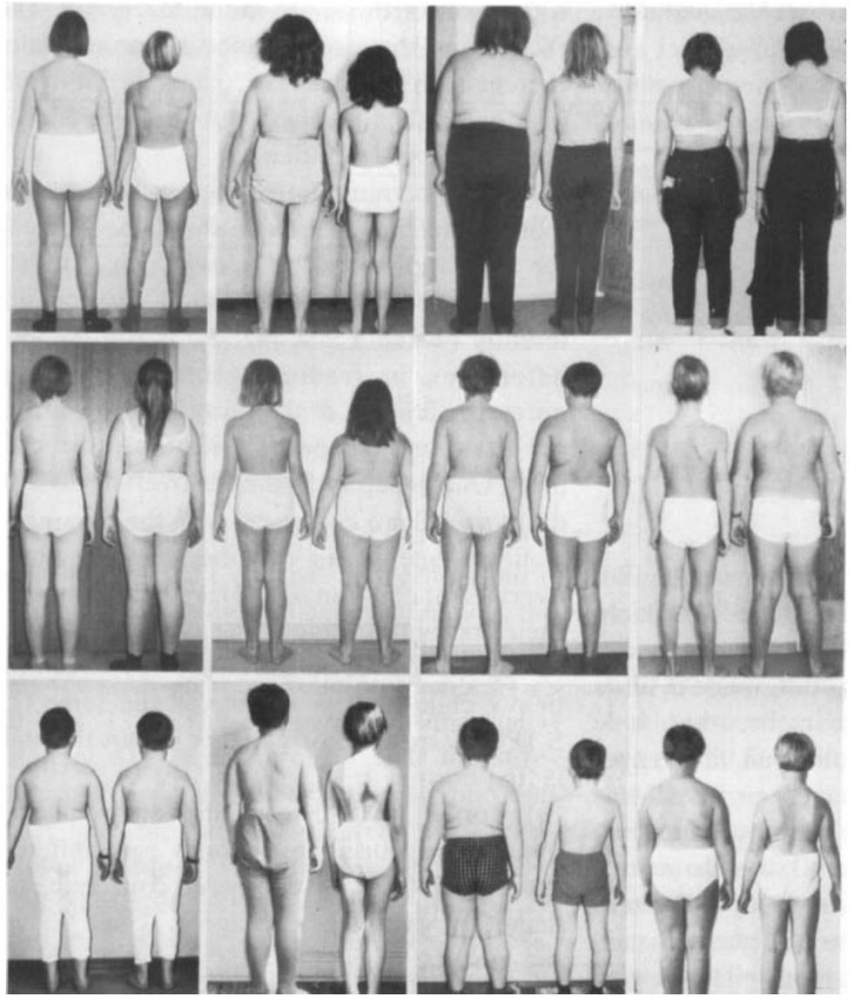
- **“Is it true that obesity is 40% to 70% genetic or inherited from parents?”. Does this mean that 40-70% of people with obesity inherit obesity from their parents?**
- **The statement derives from Twin and Adoption studies which estimate 40% to 70% of BMI variations are due to genetics**

1. Biology of weight maintenance – our genes?

1- Twin Study: The Aetiology of Obesity in Children: A study of 101 Twin Pairs (**1976**). **Borjeson, Acta Paediatr Scand 65:279**



Monozygotic Twins



Dizygotic Twins

1. Biology of weight maintenance – our genes?

1- Twin Study: The Aetiology of Obesity in Children: A study of 101 Twin Pairs (**1976**). **Borjeson, Acta Paediatr Scand 65:279**

Table 1		Number of Pairs
Reported twins		5,008
One or both twins overweight	**5%**	250
One or both twins overweight and of same sex		160
Not possible to examine		18
Refused to co-operate		4
Examined (primary material)		138
Excluded because of disease		11
Excluded because not fat enough		26
Investigation material		101

Table 5. Comparison between MZ and DZ in weight differences expressed in S.D. (M)

Twin Type	Intra-Pair Difference S.D. (M)	Twin Fathers S.D. (M)
Monozygotic (39 Twins)	0.75	2.64
Dizygotic (61 Twins)	2.36	2.86

Conclusion:

- Much less variations in-between monozygotic twins that dizygotic twins
- A major effects of genetics on BMI of twins

1. Biology of weight maintenance – our genes?

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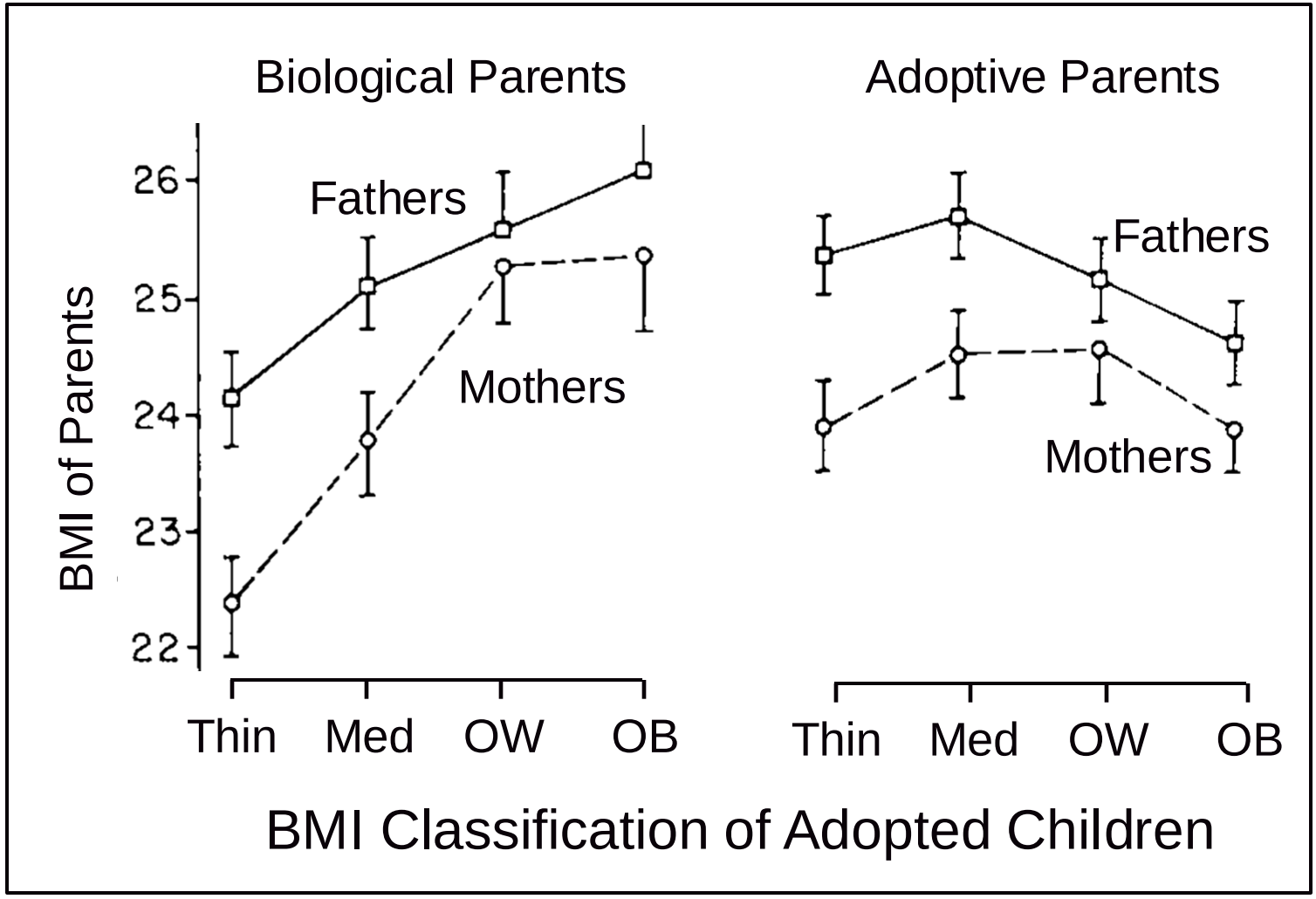
Qatar Metabolic Institute
حمد Hamad

2- Adoption Study: An Adoption Study of Human Obesity (**1986**).
Stunkard et, NEJM 314:193

BMI Classes of Adoptees	N
Thin	136
Median	137
Overweight	138
Obese	129

BMIs of adopted children correlate with biological parents BMI not with adopted parents BMI



1. Biology of weight maintenance – our genes?

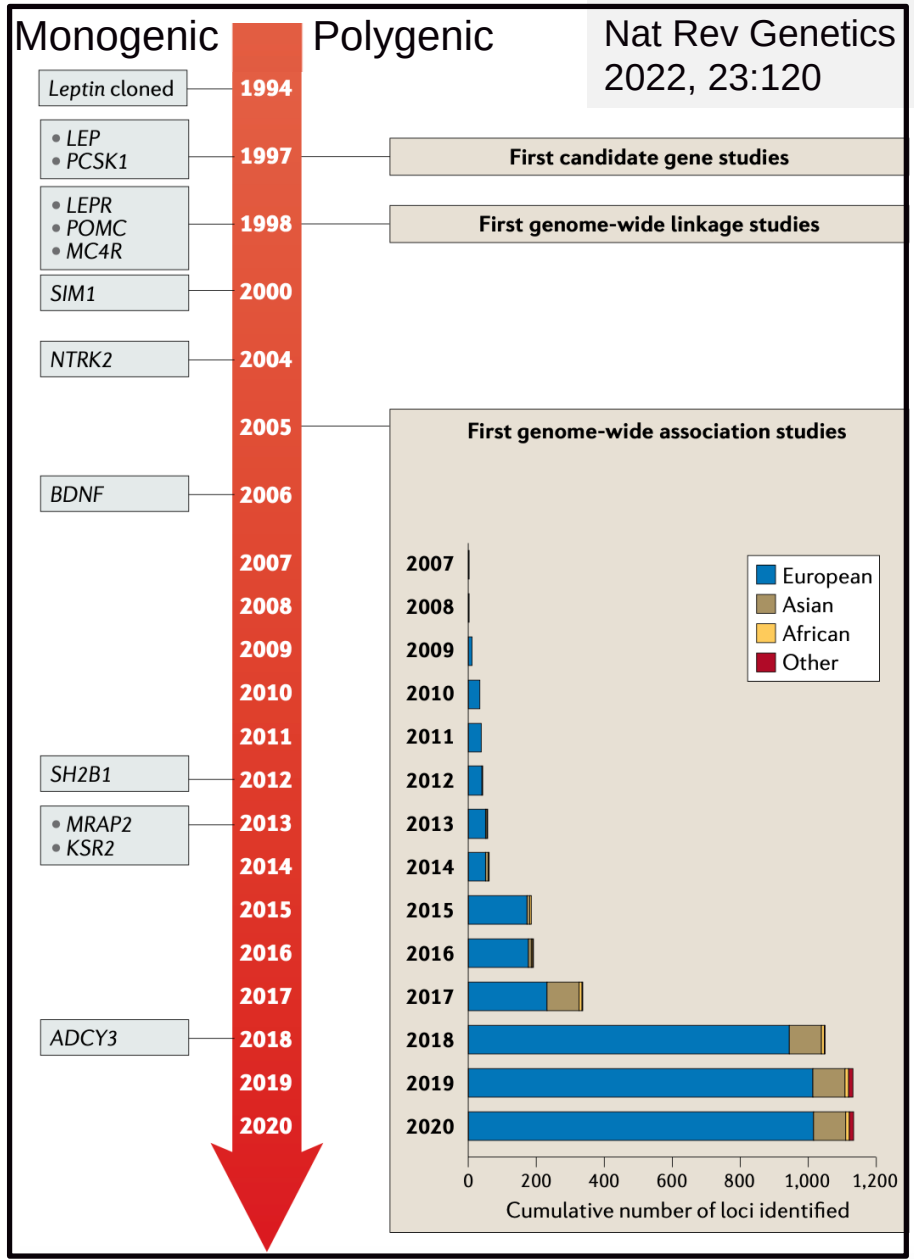
- "Is it true that obesity is 40% to 70% genetic or inherited from parents?". Does this mean that 40-70% of people with obesity inherit obesity from their parents?
- The statement derives from Twin and Adoption studies which estimate BMI variations to be 40% to 70% among twins
- **Twin studies show that: "if a twin develops obesity, the likelihood for the other twin to develop obesity is 40-70%. If a twin remains lean, the likelihood of the other twin to remain lean is 40-70%" (AJCN 2016,104:371).**
- **Adoption studies show that "BMI of adopted children correlates with that of biological parents not adopted parents".**
- **Twin and Adoption studies do not imply that 40-70% of people with obesity inherited obesity from parents.**

1. Biology of weight maintenance – our genes?

Genetics of common obesity:

- GWAS of ~800,000 individuals, identified >750 loci, with MAFs as small as 1.6% and per-allele effects as low as 0.04 kg/m2 per allele (~120 g / 1.7 m person).
- **Combined, these loci explain 6% of BMI variations.**

- **MC4R variations has a prevalence of 7.3% in general population (Namou et al. IJO 2021) – not all are pathologic.**



1. Biology of weight maintenance – our genes?

Nat Rev Genetics
2022, 23:120

Does polygenic score predict obesity?

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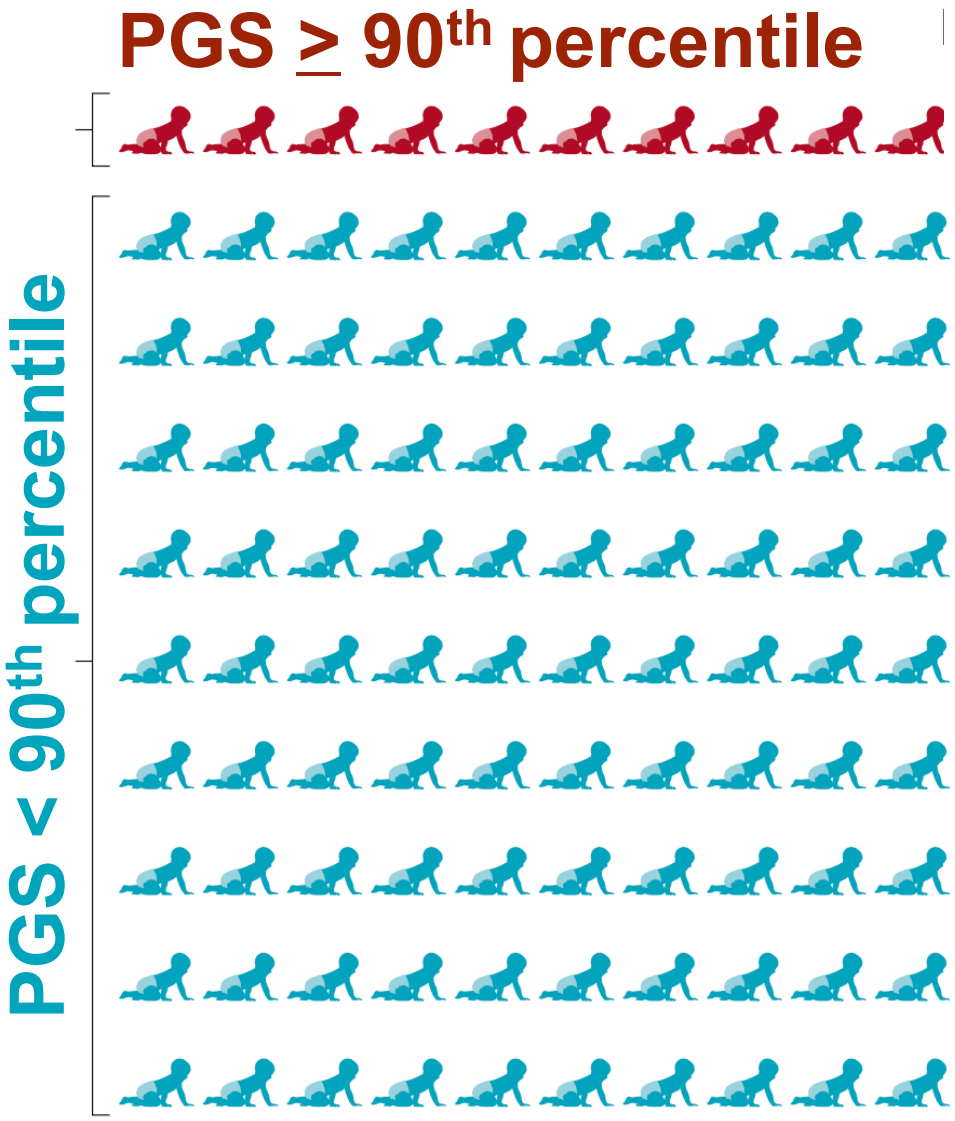

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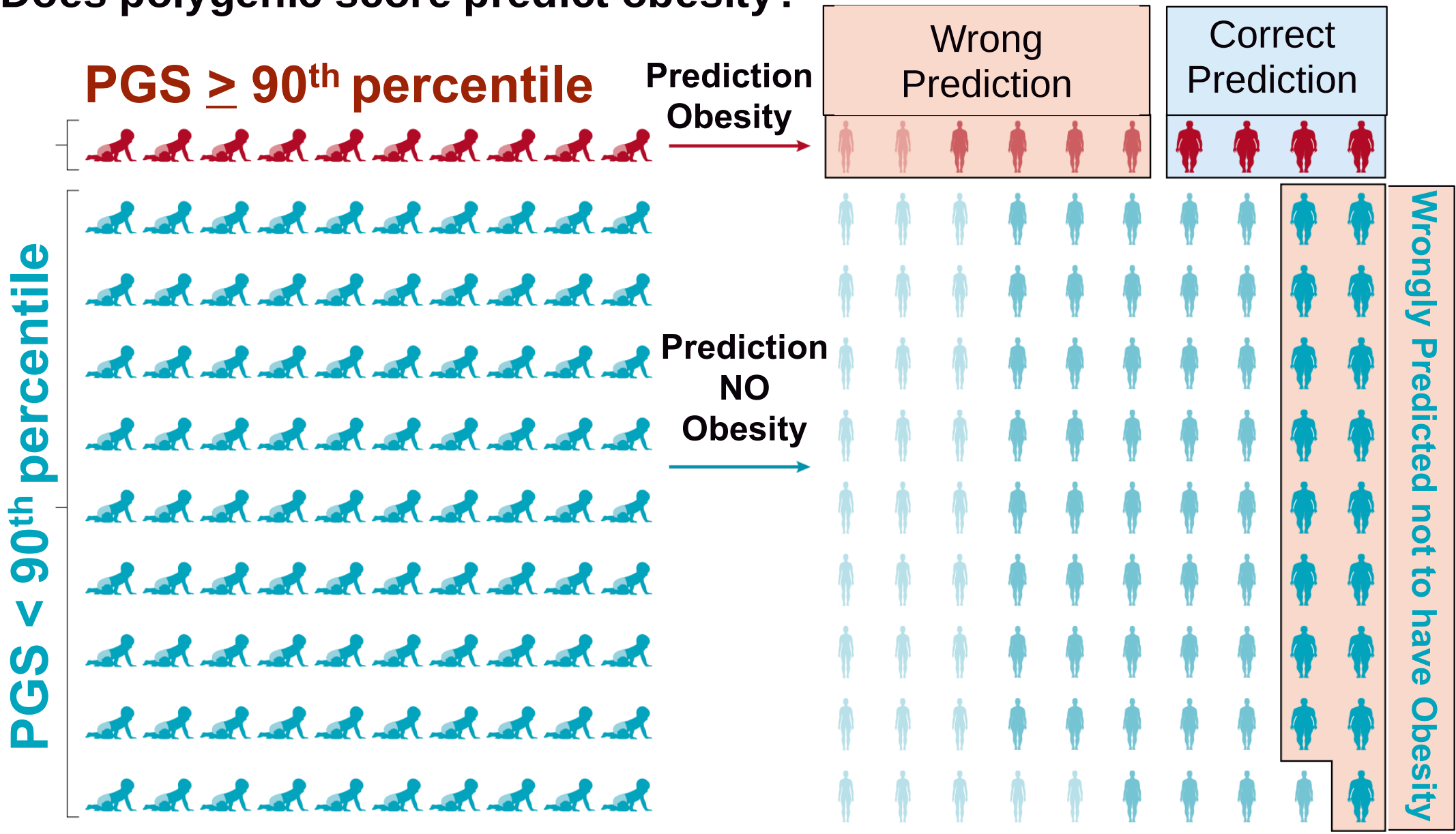
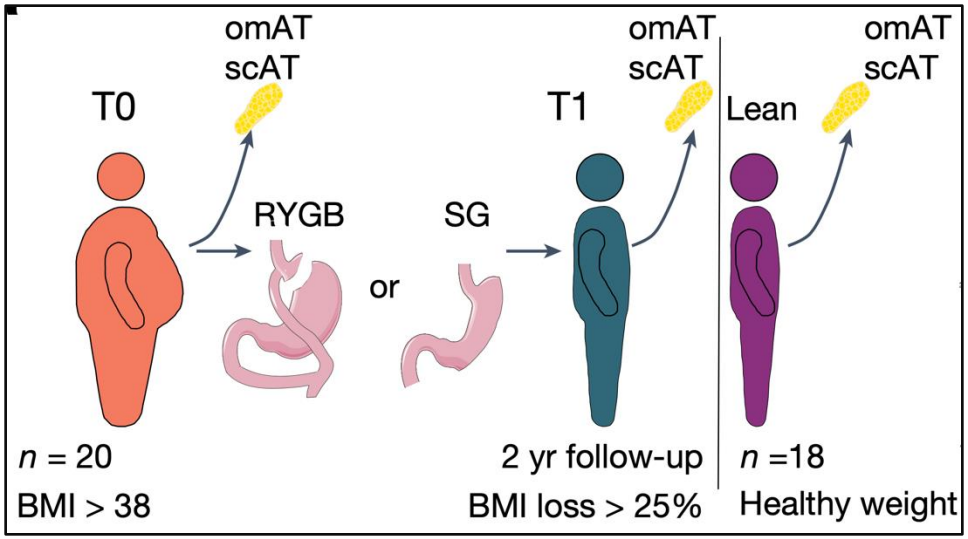


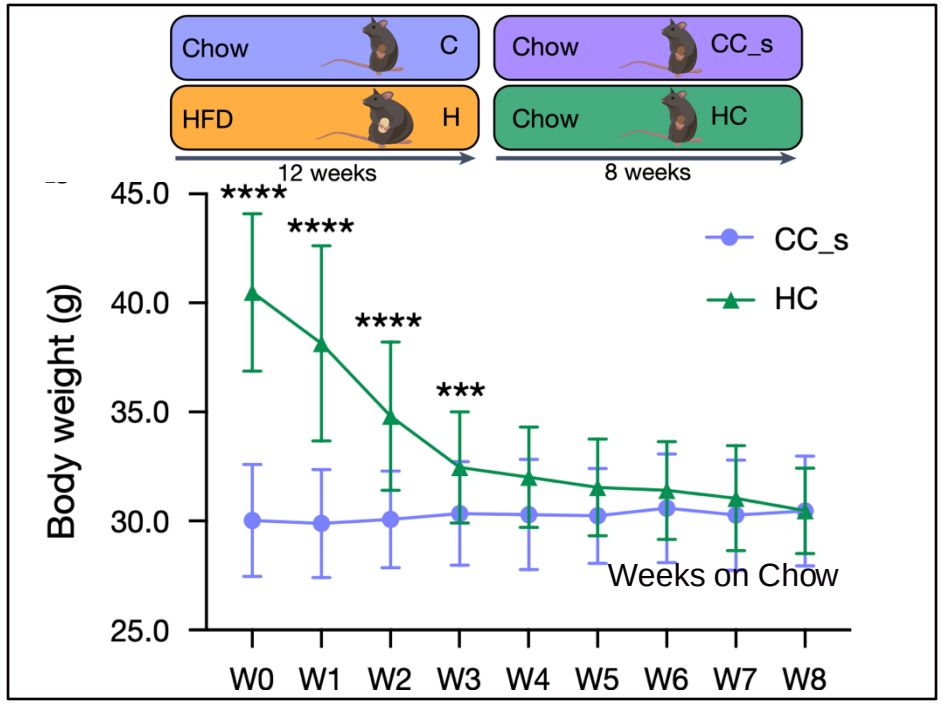
1. Biology of weight maintenance – our genes?

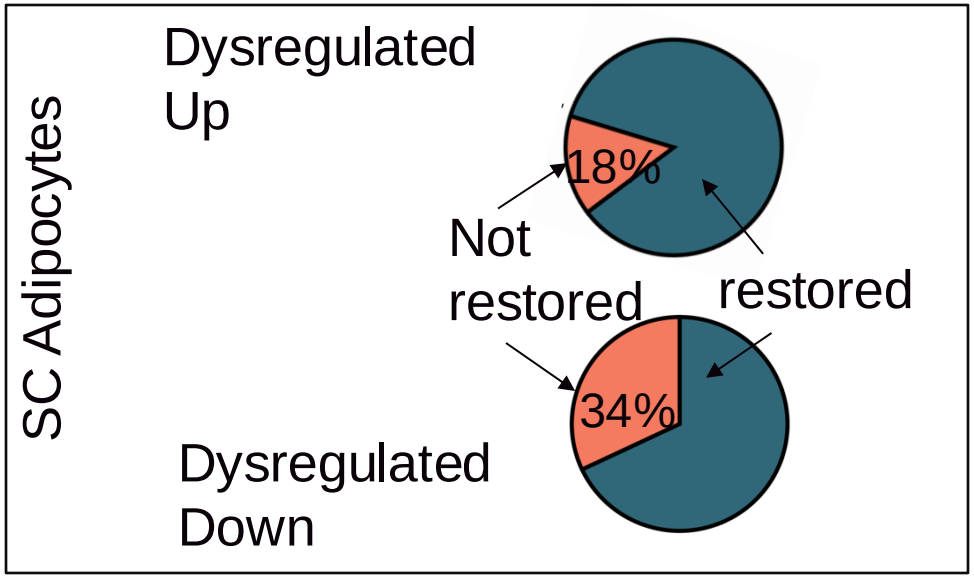
- **Only 40% of people with high polygenic obesity risk score (defined as >90th percentile) develop BMI≥30. They represent about 15-20% of people with obesity.**
- **Most people with obesity (80-85%) do not have a high polygenic obesity risk score**
- **The main cause of the obesity epidemic is not the emergence of new genetic mutations. Modern life with food abundance & reduced physical activity are to blame.**
- **Obesity genes are potential therapeutic target(s).**

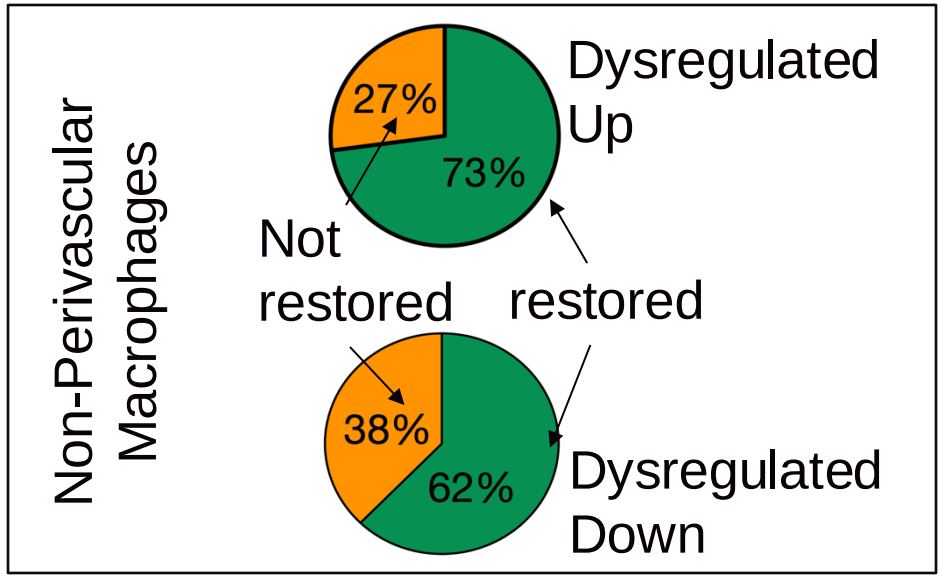
1. Biology of weight maintenance – epigenetics?

Adipose tissue retains epigenetic memory of obesity after weight loss ***Hinte et al. Nature 2024***









1. Biology of weight maintenance – our genes?

"Genetics predisposes to obesity, unhealthy lifestyle triggers obesity, epigenetics maintains obesity".

- **Unhealthy lifestyle causes obesity in people regardless of obesity genetic risk score**
- **Healthy lifestyle prevents obesity in people with high genetic risk**
- **Epigenetic modifications → persistence of obesity and resistance to treatment**

2. Behavior & body weight – social influences

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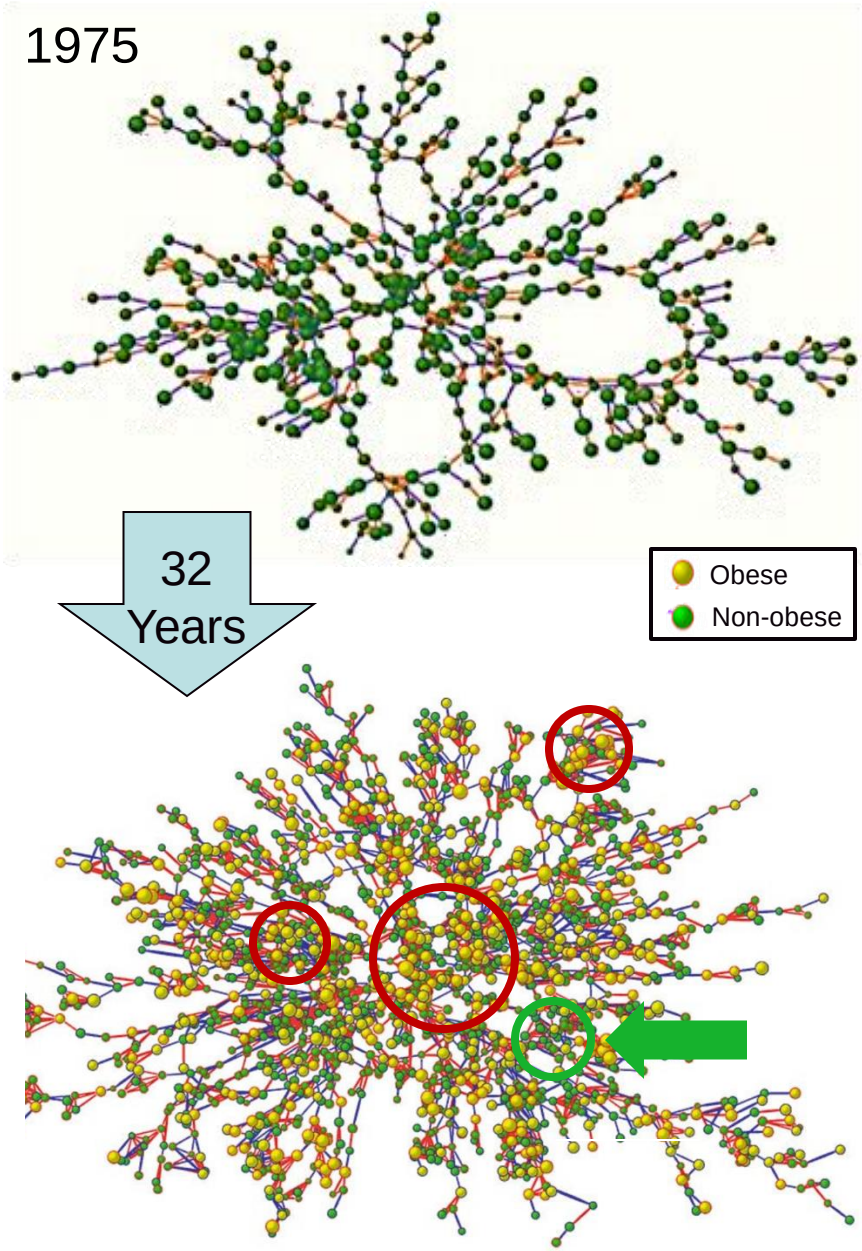
The Spread of Obesity in a Large Social Network Over 32 Years.
NEJM 2007

- 12067 people from the Framingham cohort followed over 32 years
- BMI every 5 years and social connections were determined

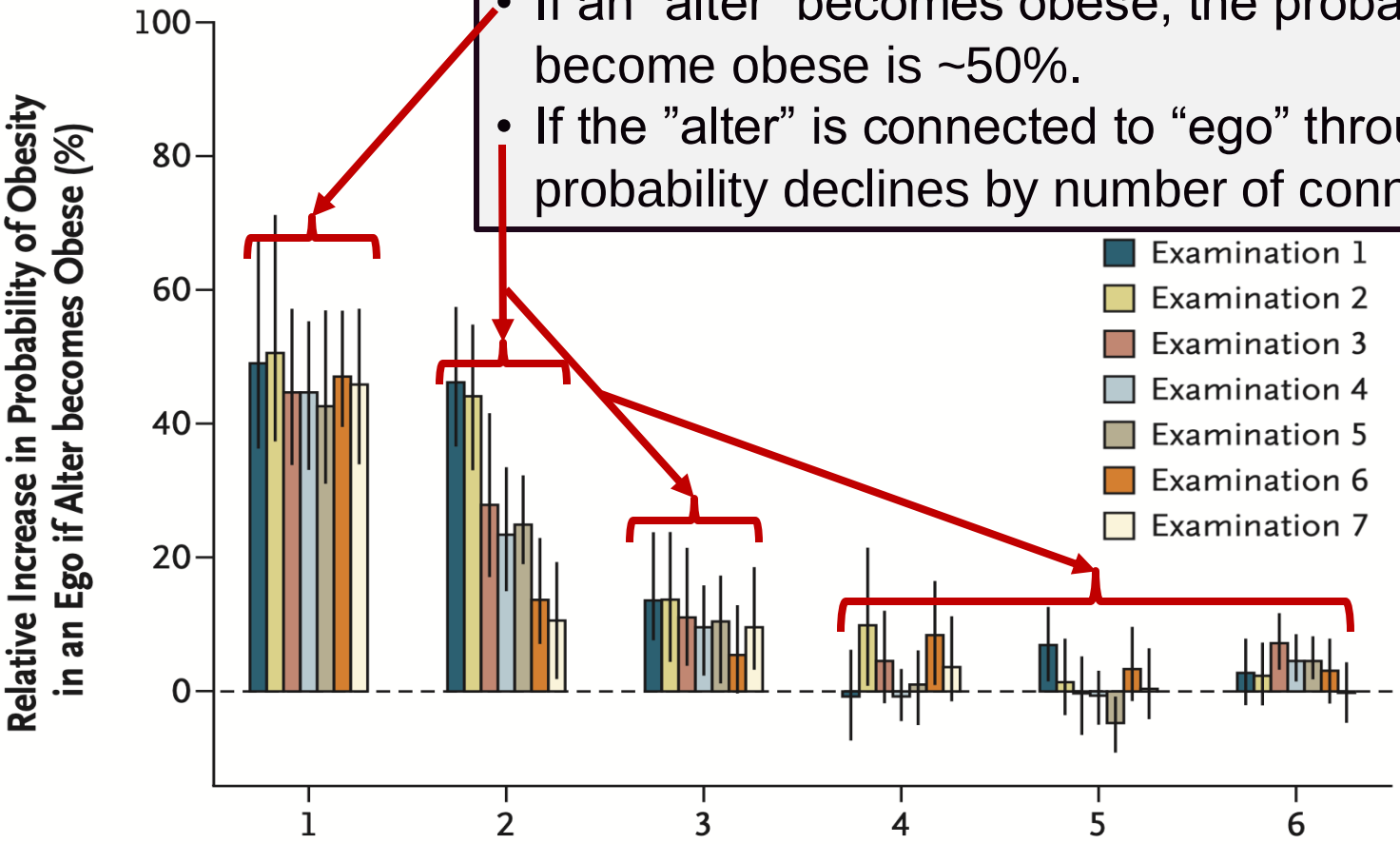


- Overtime, most people develop obesity.
- Obesity clusters followed the strength of social connections.
- **Few clusters of people without obesity**
- **BMI of people is influenced by their social connections !!**

2. Behavior & body weight – social influences

Probability of obesity in a person (**ego**) if his/her social connections (**alter**) become obese.

- If an “alter” becomes obese, the probability of an “ego” to become obese is ~50%.
- If the ”alter” is connected to “ego” through other persons, the probability declines by number of connections

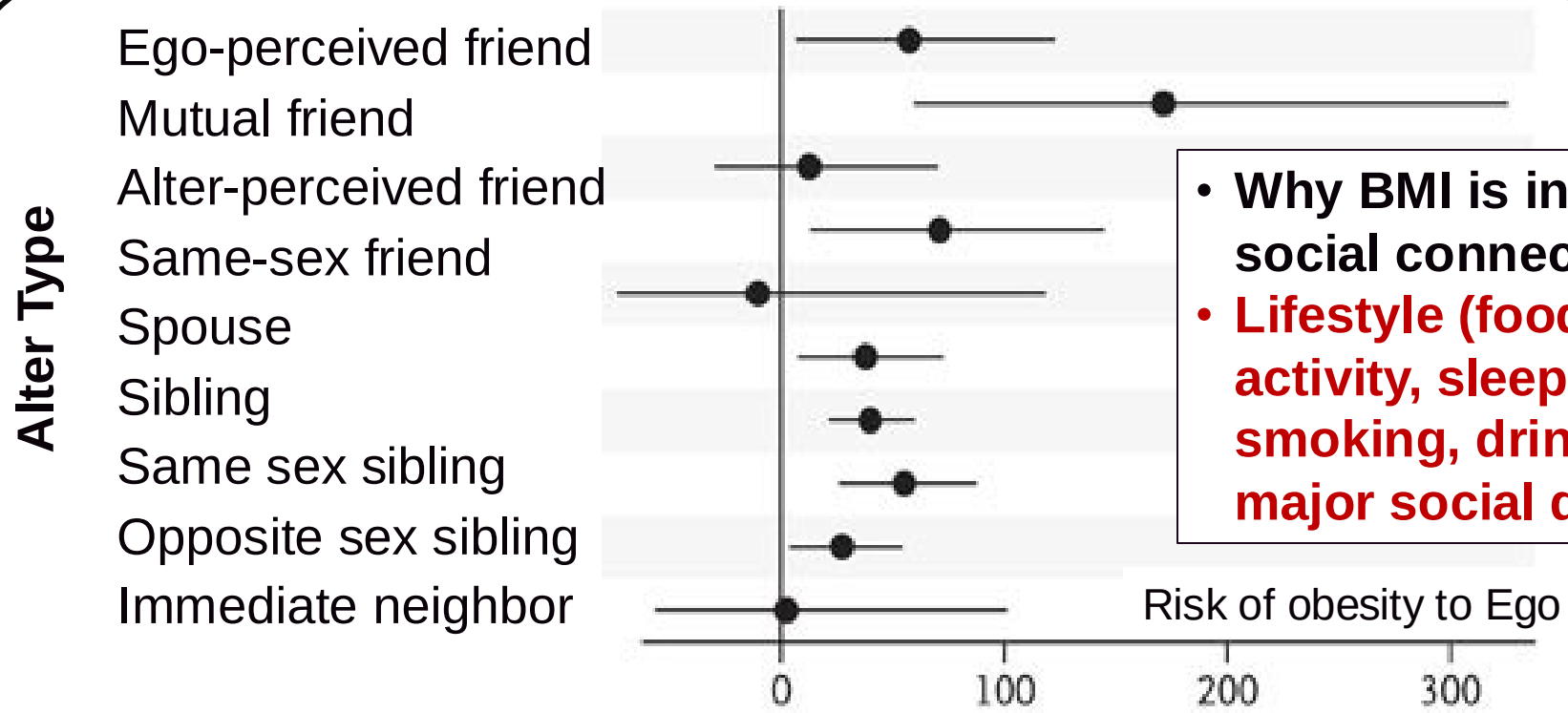


Definitions:
Ego: person being studied
Alter: person connected to Ego (friend, a family member, other)

Degree of separation = 1 if direct connection, **2 to 6** if through others.

2. Behavior & body weight – social influences

Probability of obesity in a person (**ego**) if his/her social connections (**alter**) become obese.



- **Why BMI is influenced by social connections?**
- **Lifestyle (food, physical activity, sleep habits, smoking, drinking, etc.) has major social determinants!**

Definitions
- **Ego - The person whose behavior is being analyzed.**
- **Alter - A person connected to the ego**

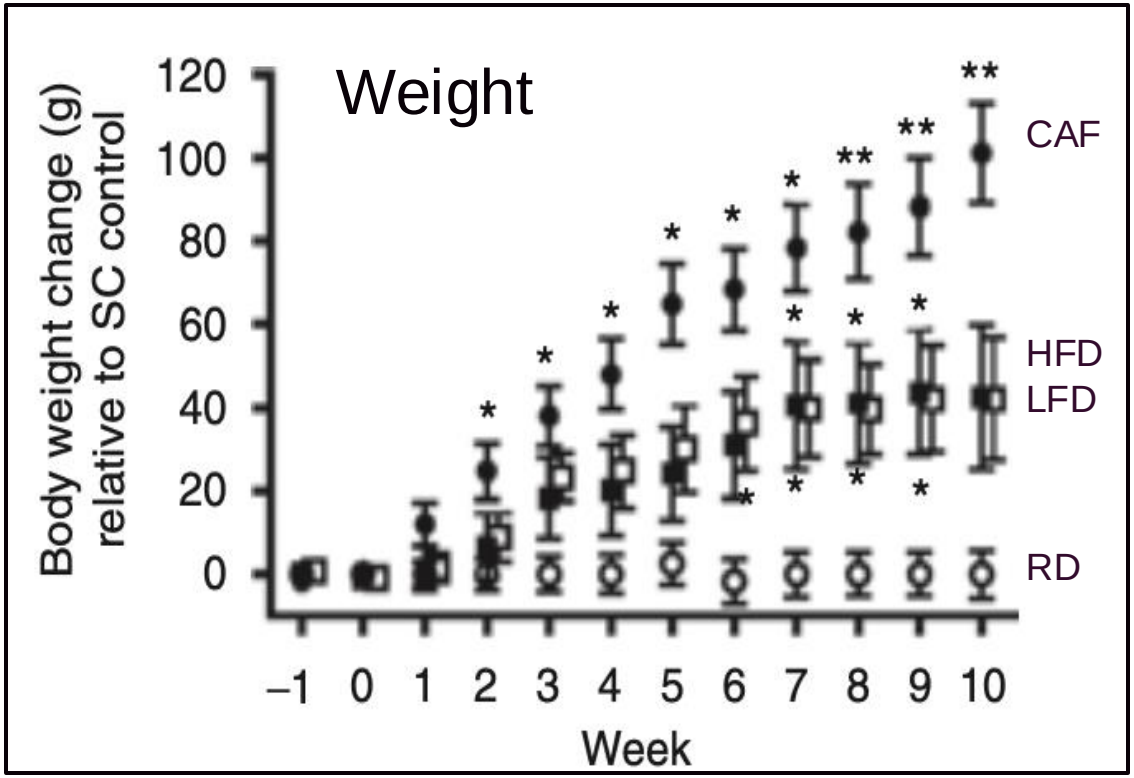
2. Behavior & body weight – Hedonic Eating

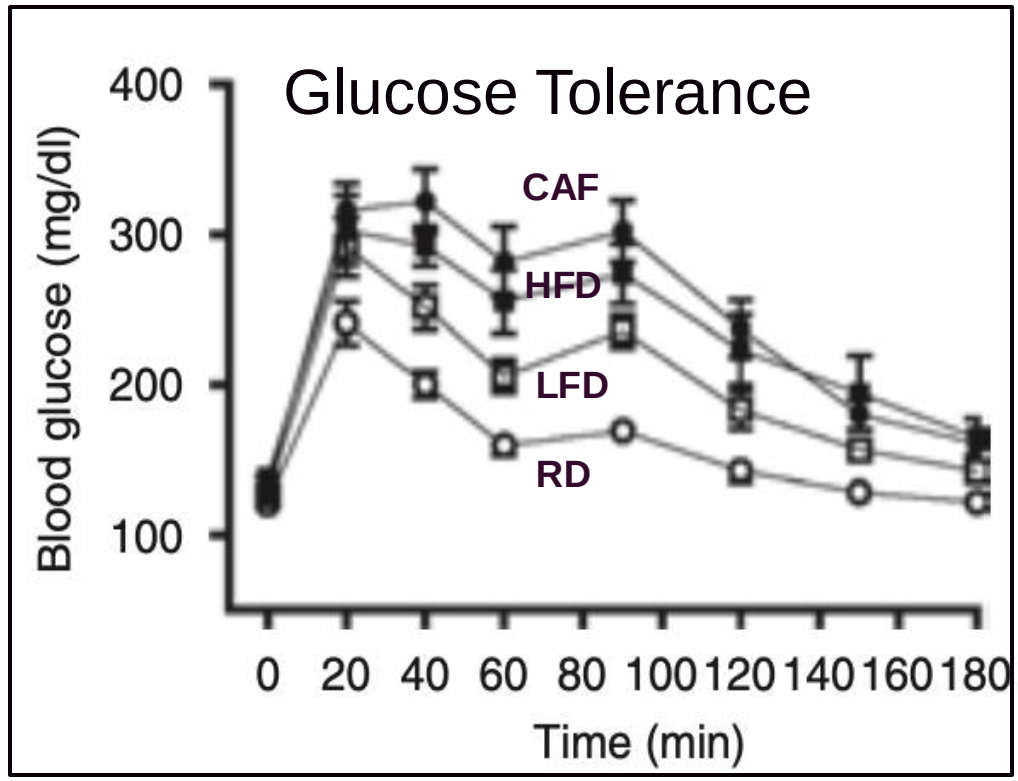
Cafeteria Diet: a Robust Model of Met Sd: *Sampey et al,* ***Obesity 2011, 9:1109***

Even rats have a sweet tooth !!!!!!

2. Behavior & body weight – Hedonic Eating

Cafeteria Diet for Rats? "cookies, cereals, cheese, processed meats, crackers"





- CAFD, HFD and LFD → more calories consumed → increased weight
- Glucose intolerance is associated with all 3 diets, worse in the CAF diet
- Insulin secretion is higher and response to insulin is lower
- **Taste of food disturbs energy balance!**

***Obesity* (2011) 19, 1109–1117**

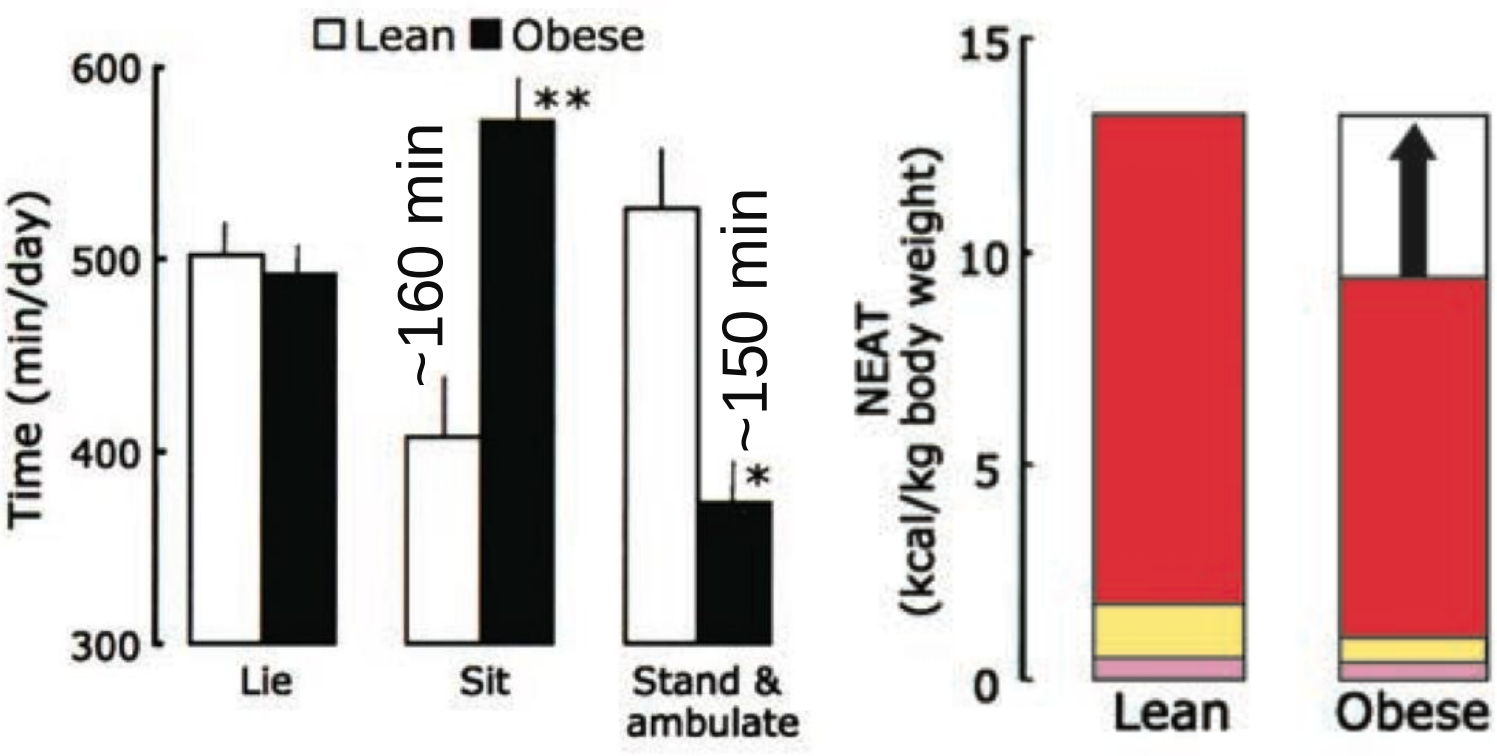
2. Behavior & body weight – Sedentary Life

None Exercise Ambulatory Thermogenesis (NEAT)

Levine et al. Science 2005

Body movements measured every ½ second in 20 individuals (10 lean and 10 with obesity):

- Individuals with obesity sit ~160 min a day more than leans
- Individuals with obesity expend ~350 less calories per day in NEAT



If subjects with obesity adopt the NEAT-behavior of lean individuals, they may expend an extra 350 kcal per day!!!

3. Public Health and Obesity

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103 processes energy balance

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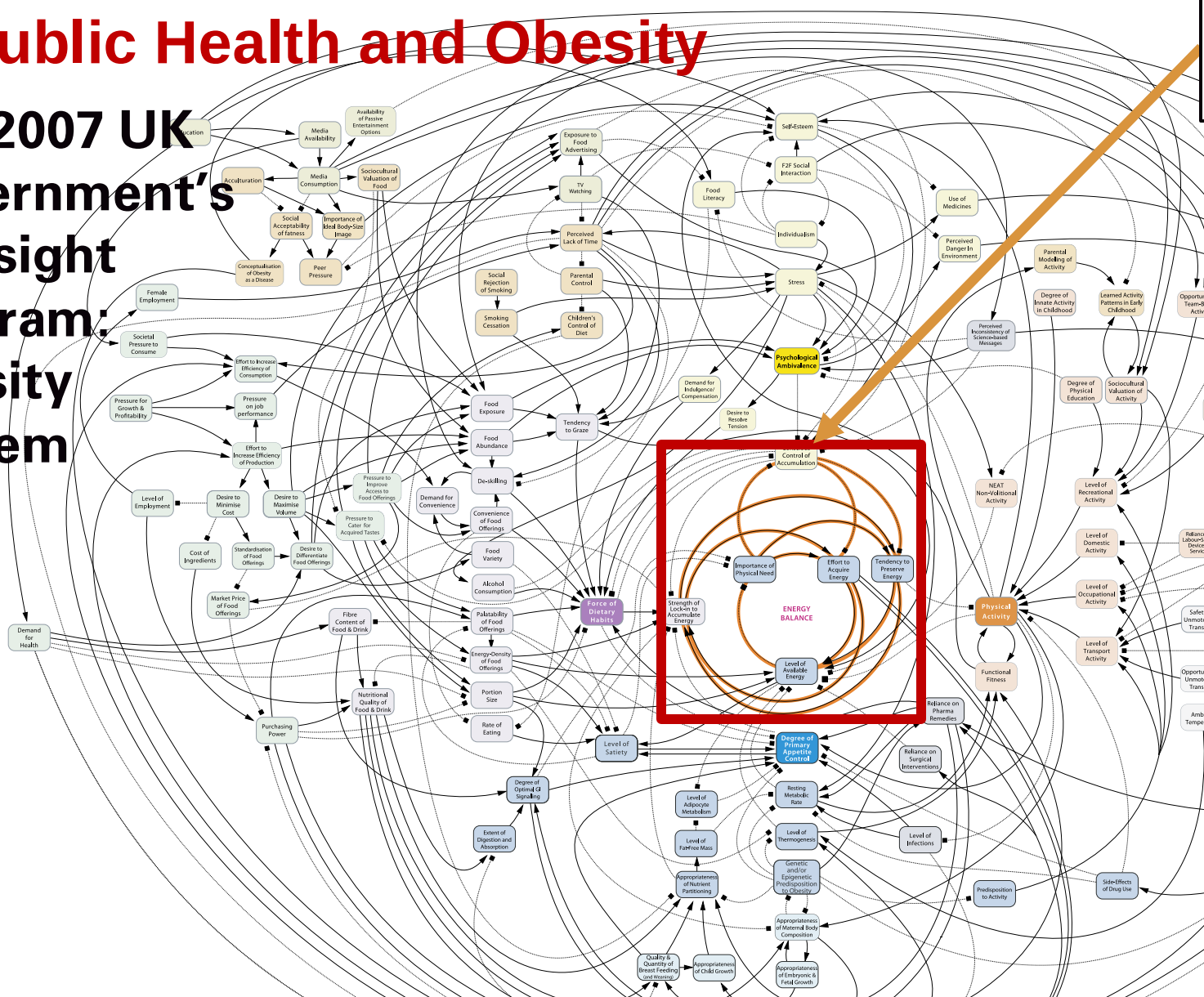
Qatar Metabolic Institute

حمد Hamad

Variable		Variable		Variable	
Alcohol consumption—	15 processes Food consump-tion	Degree of innate activity in childhood	11 processes Individual physical activity	Appropriateness of child growth	19 processes Physio-logy
Convenience of food offerings		Degree of physical education		Appropriateness of embryonic & fetal growth	
De-skilling		Functional fitness		Appropriateness of maternal body composition	
Demand for convenience		Learned activity patterns in early childhood		Appropriateness of nutrient partitioning	
Energy-density of food offerings		Level of domestic activity		Degree of optimal GI signalling	
Fibre content of Food & Drink—		Level of occupational activity		Degree of primary appetite control by brain	
Food abundance		Level of recreational activity		Extent of digestion and absorption	
Food exposure		Level of transport activity		Genetic and/or epigenetic predisposition to obesity	
Food variety		Non-volitional activity (NEAT)		Level of adipocyte metabolism	
Force of dietary habits		Parental modelling of activity		Level of fat-free mass	
Nutritional quality of Food & Drink—		Physical activity		Level of infections	
Palatability of food offerings—		Demand for indulgence/compensation	10 processes Individual psycho-logy	Level of satiety	
Portion size—		Desire to resolve tension		Level of thermogenesis	
Rate of eating		F2F social interaction		Predisposition to activity—	
Tendency to graze		Food literacy		Quality & Quantity of breast feeding—	
Cost of ingredients	18 processes Food produc-tion	Individualism		Reliance on pharma remedies—	
Demand for health—		Perceived inconsistency of science-based messages		Reliance on surgical interventions	
Desire to differentiate food offerings		Psychological ambivalence		Resting metabolic rate	
Desire to maximise volume		Self esteem		Side-effects of drug use—	
Desire to minimise cost		Stress		Acculturation	18 processes Social psycho-logy
Effort to increase efficiency of consumption		Use of medicines—		Availability of passive entertainment options	
Effort to increase efficiency of production		Accessibility to opportunities for physical exercise	12 processes Physical activity environ-ment	Children's control of diet	
Female employment—		Ambient temperature		Conceptualisation of obesity as a disease	
Level of employment—		Cost of physical exercise		Education—	
Level of female employment—		Dominance of motorised transport		Exposure to food advertising—	
Market price of food offerings—		Dominance of sedentary employment		Importance of ideal body-size image	
Pressure for growth and profitability		Opportunity for team-based activity—		Media availability	
Pressure on job performance		Opportunity for unmotorised transport		Media consumption	
Pressure to cater for acquired taste		Perceived danger in environment—		Parental control	
Pressure to improve access to food offerings		Reliance of labour-saving devices		Peer pressure	
Purchasing power—		Safety of unmotorised transport		Perceived lack of time	
Societal pressure to consume		Social depreciation of labour		Smoking cessation	
Standardisation of food offerings		Walkability of living environment—		Social acceptability of fatness—	
				Social rejection of smoking—	
				Sociocultural valuation of food	
				Sociocultural valuation of physical activity	
				TV watching Time spent watching TV	

3. Public Health and Obesity

The 2007 UK Government's Foresight Program: Obesity System Map



The Energy Balance Engine

- Conscious Control of Energy Accumulation
- Tendency to Preserve Energy
- Effort to Acquire Energy
- Importance of Physical Need
- Strength of Lock-in to accumulate Energy
- Level of Available Energy

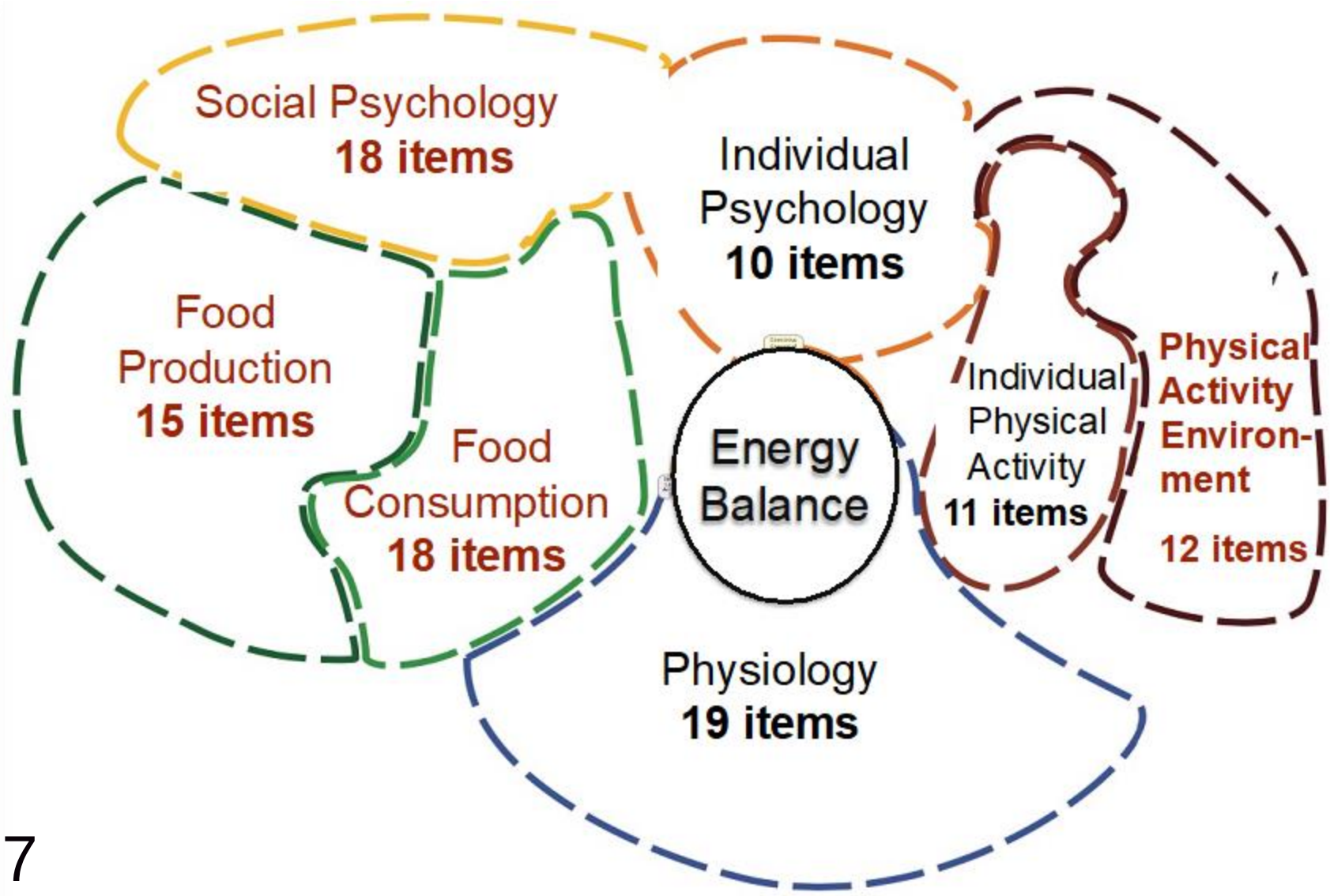
Med
Social
Psychological
Economic
Food
Activity
Infrastructure
Developmental
Biological
Medical

Positive Influence

The map assumes human body as an "Engine": 103 processes influence energy balance of the "Engine"

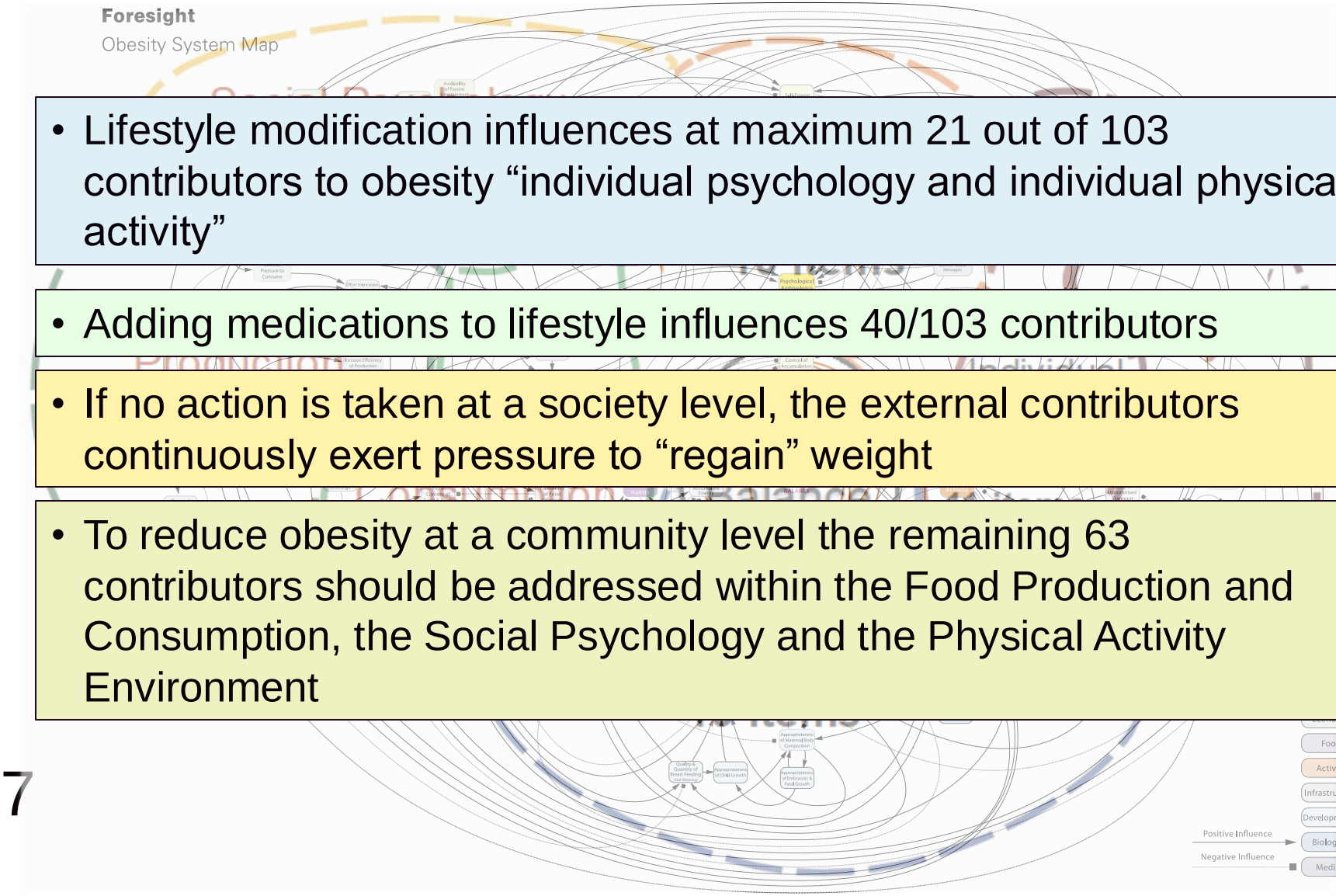
3. Public Health and Obesity

Obesity System Map (UK Foresight Program): 103 processes influence energy balance mapped to 7 domains



3. Public Health and Obesity

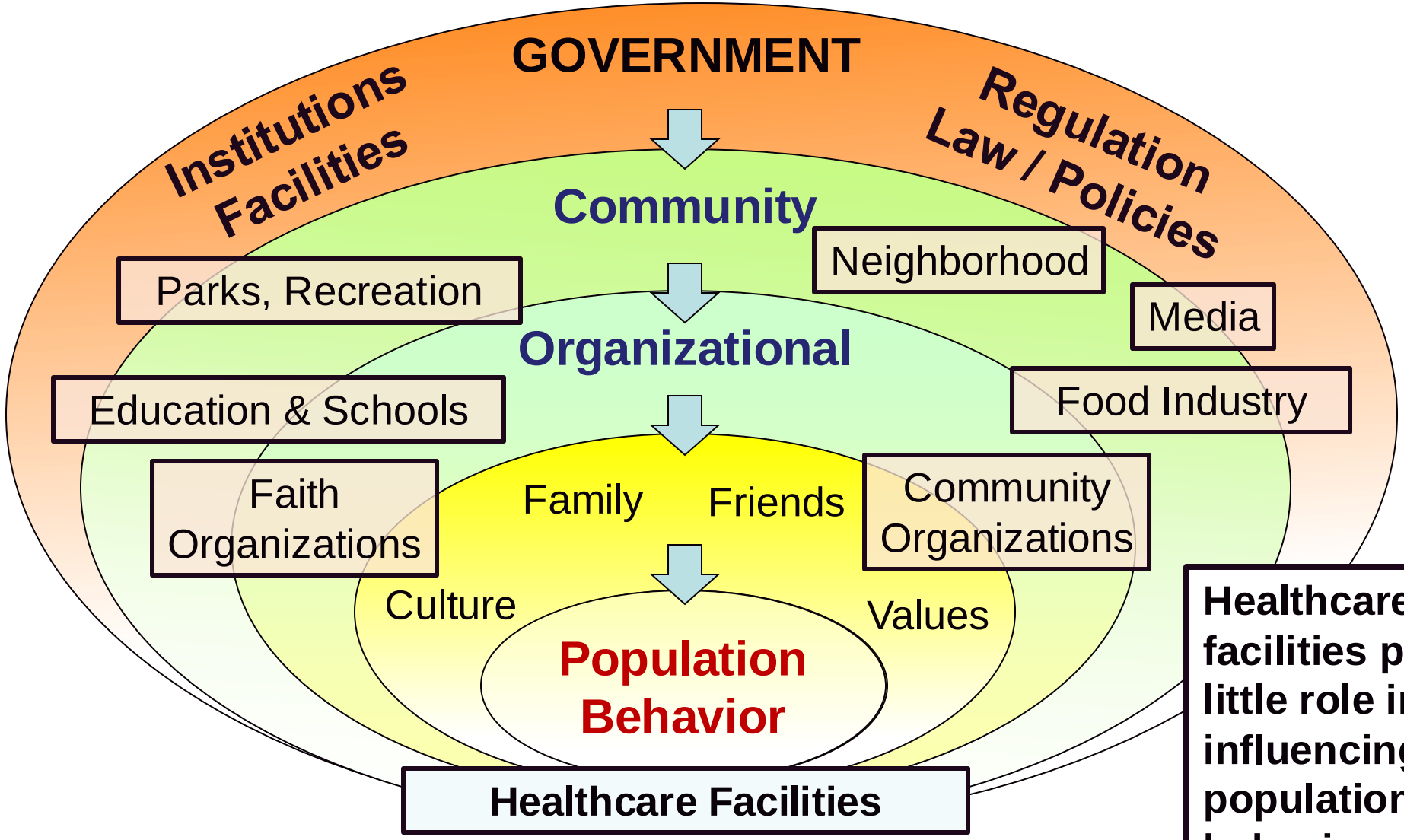
Obesity System Map (UK Foresight Program): 103 processes influence energy balance mapped to 7 domains



- Lifestyle modification influences at maximum 21 out of 103 contributors to obesity “individual psychology and individual physica activity”
- Adding medications to lifestyle influences 40/103 contributors
- If no action is taken at a society level, the external contributors continuously exert pressure to “regain” weight
- To reduce obesity at a community level the remaining 63 contributors should be addressed within the Food Production and Consumption, the Social Psychology and the Physical Activity Environment

3. Public Health and Obesity

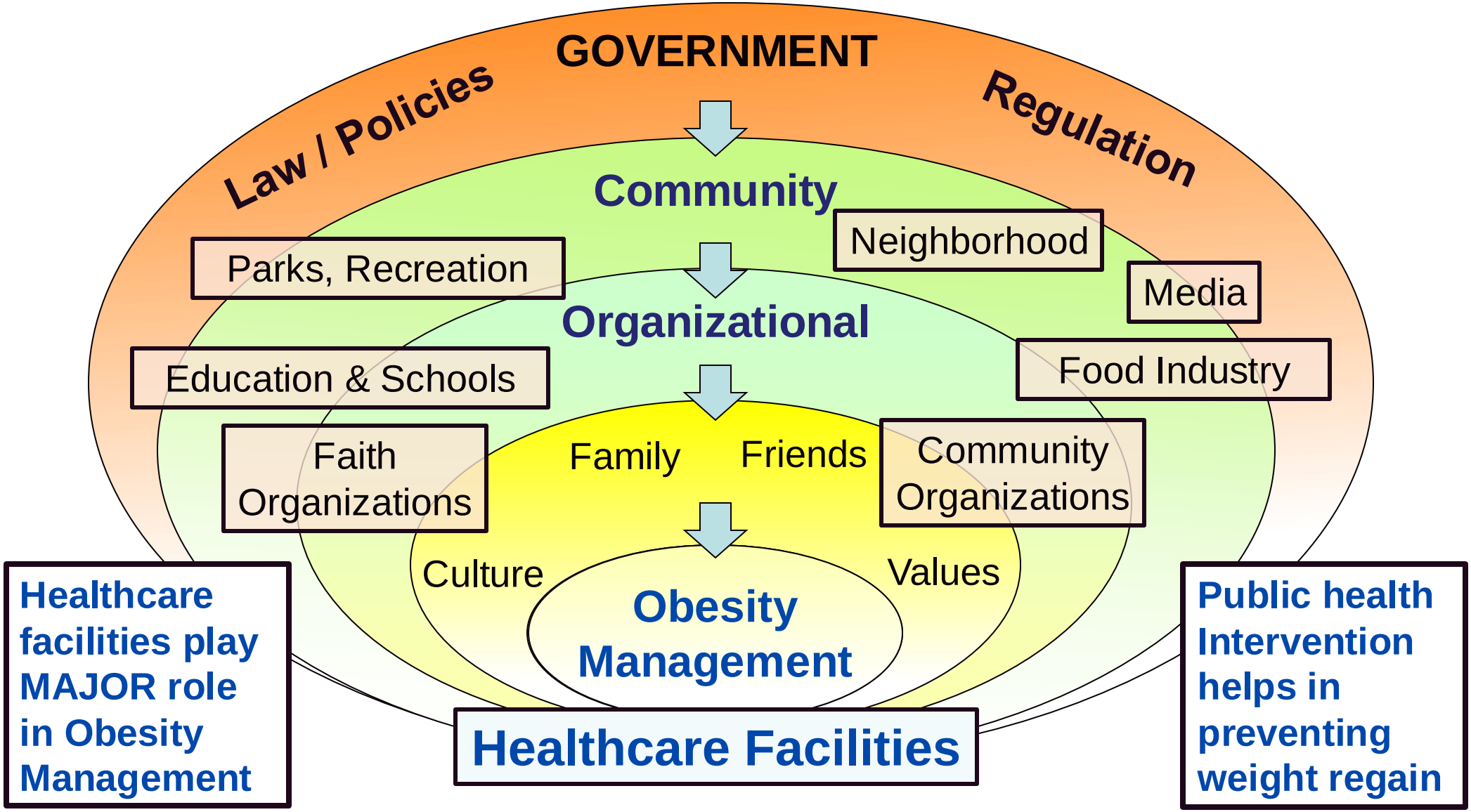
Comprehensive Approach to the Prevention of Obesity



Healthcare facilities play little role in influencing population behavior

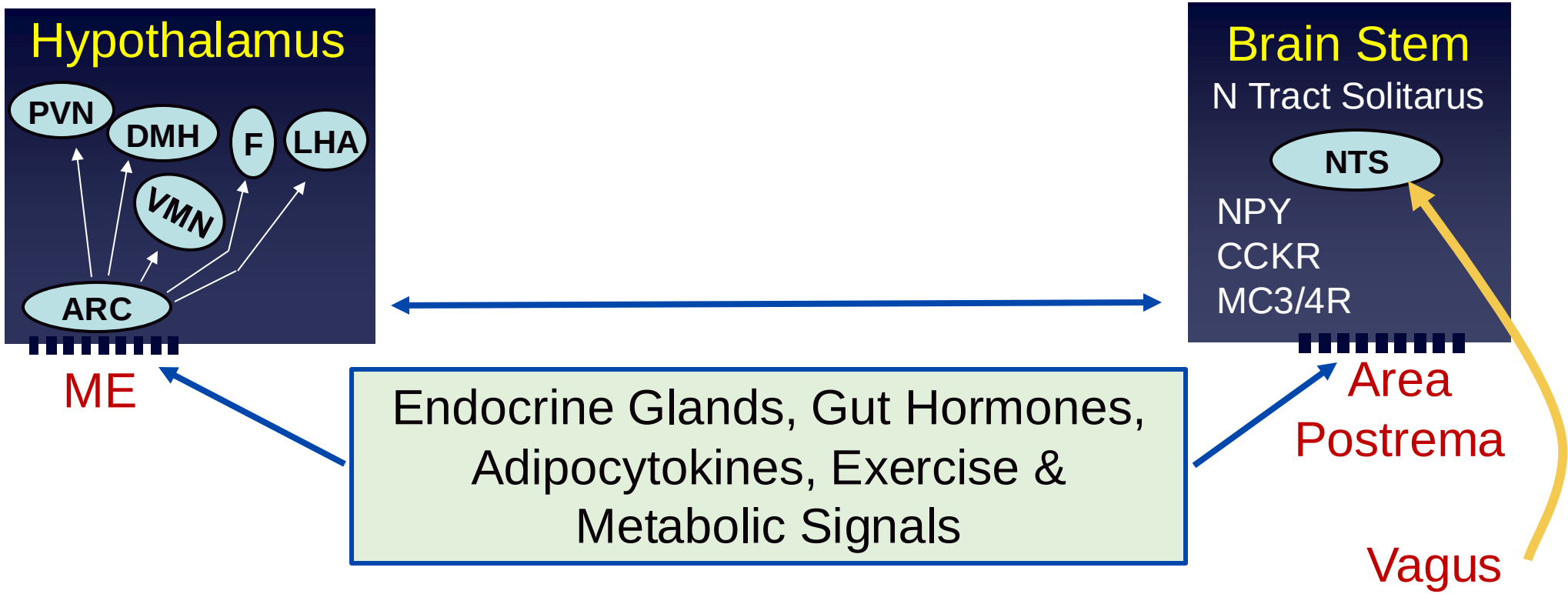
3. Public Health and Obesity

Comprehensive Approach to the Management of Obesity

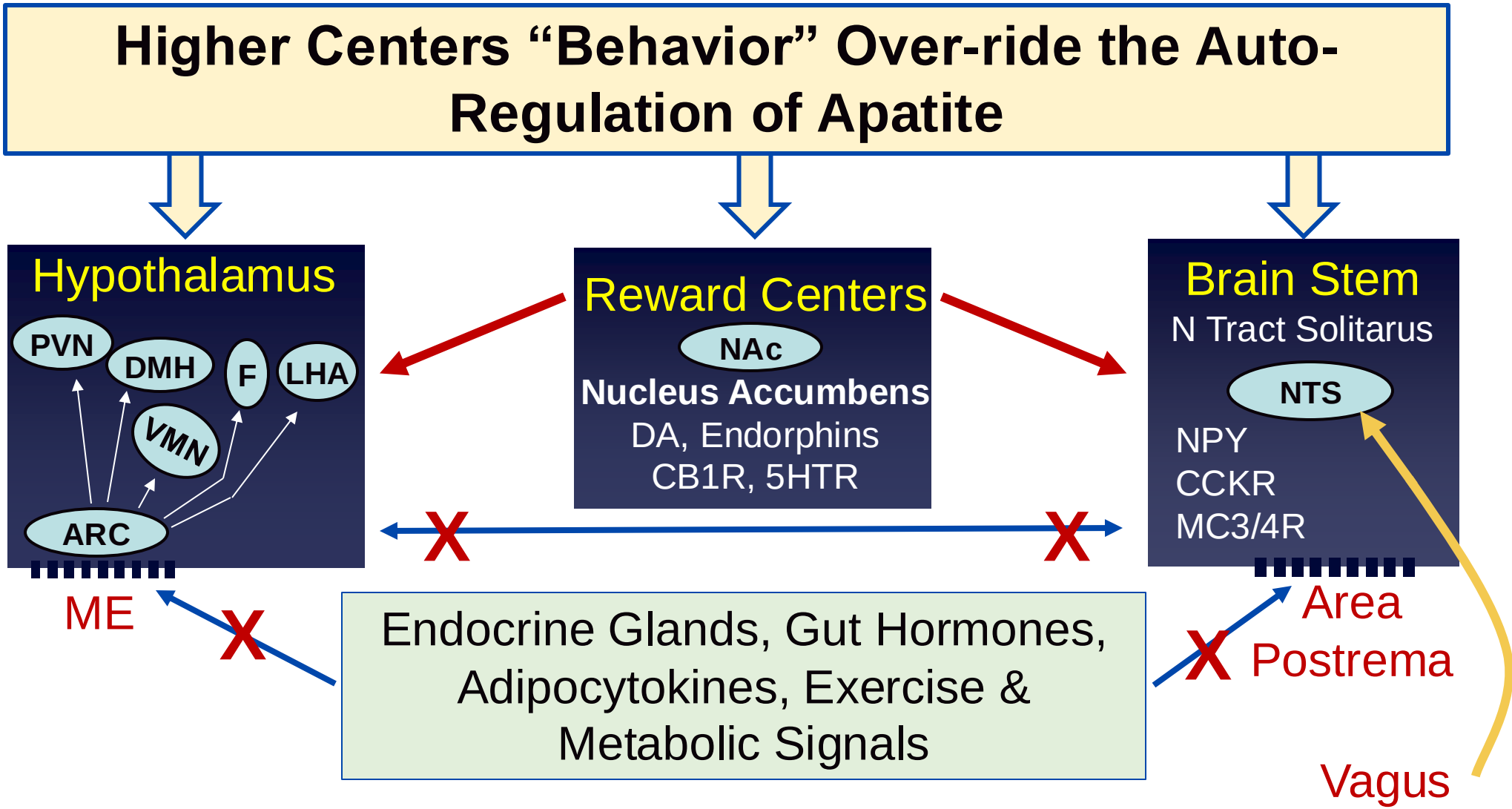


Regulation of Appetite & BMR

"Neuro-Endocrine-Gut" Circuits → Auto-Regulation of Apatite & BMR Based on Physiological Needs (Genetically-Determined) with individual variations

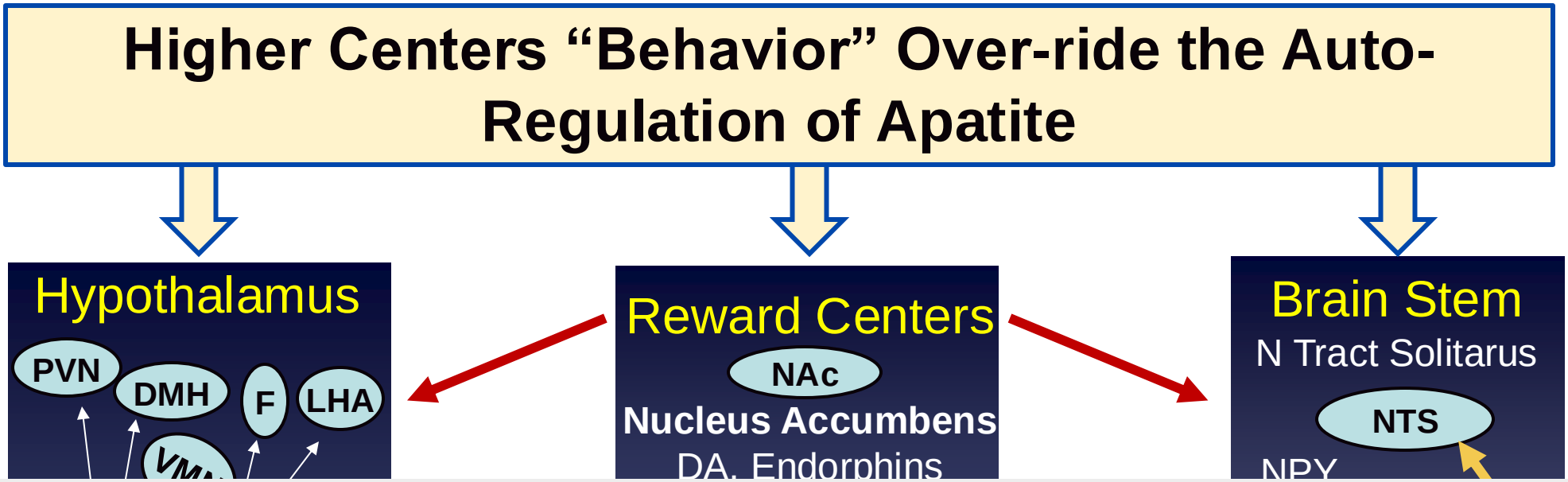


Regulation of Appetite & BMR



Regulation of Appetite & BMR

المعهد الوطني للسكري
والسمنة وأمراض الأيض
Qatar Metabolic Institute
حمد Hamad



We often eat not because of physiological needs:

- **We eat with friends and family to entertain social interactions**
- **We eat because foods look, taste and/or smell nice and different**
- **We eat because we are depressed (or excited!).**
- **We often eat "out" or buy "ready to eat" food**
- **Our genes became "imprinted" with obesogenic environment and "locked" in the "chronic obesity syndrome" (epigenetics)**


Thank
you