

بنام خداوند بخشنده و مهربان

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Defining Obesity



The word "obesity" (from the Latin *obesitas*)

Obesitas is the condition of the *obesus* :

Ob = over , *Esus* = to eat

Defining Obesity

*"The excess accumulation of fat
(adipose tissue) throughout the body"*

Male : 12- 18% , > 22%
Female : 20 – 30% , > 32%

Obesity no longer limited to the US

- 1.6 billion people world wide are at least overweight
- Almost 25% of people in the UK are overweight or obese.
- Even Asian countries are noticing and increase
- One can be obese yet malnourished

Excess body fat accumulate when people consistently take in more food energy than they need .

Why they do this? Is it:

Genetic?

Environmental?

Cultural?

Behavioral?

Socioeconomic?

Psychological?

Metabolic?

All of these?

Syndemic

Original definition: two or more diseases that interact in time and place, negatively affect each other and have common economic, societal, or environmental drivers

Example: Intravenous drug use, HIV and hepatitis C infections

The Global Syndemic

- *Definition: the interactions of the pandemics of obesity, undernutrition, and climate change in time and place, negatively affect each other, and have common economic, societal, or environmental drivers*
- *Considered climate change as a pandemic*
- *Driven by food, transport, urban design, and land use systems*
- *Population rather than individual focused*

Examples of Interactions

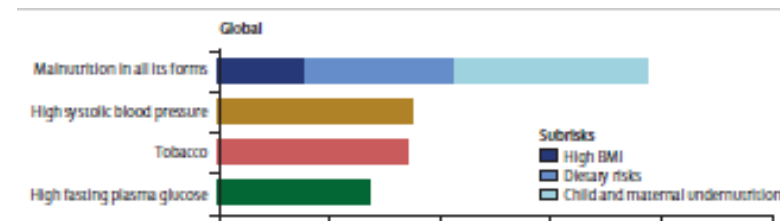
- *Obesity and stunting in the same children and same population*
- *LBW and adult obesity*
- *Car use, inactivity, and GHG emissions*
- *Cattle production, GHG emissions, meat consumption and colon cancer, CVD, and obesity*
- *GHGs, climate change, catastrophic weather events, and reduced agricultural production and food nutrients, especially in marginal areas, leading to hunger and undernutrition*

At every stage of development, malnutrition in all its forms is the highest risk for ill-health and premature death

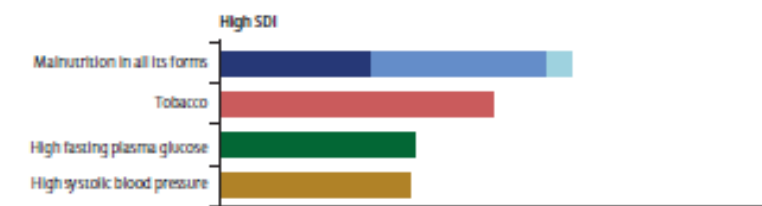
Type of malnutrition differs by stage of development

A. Ashfin, personal communication

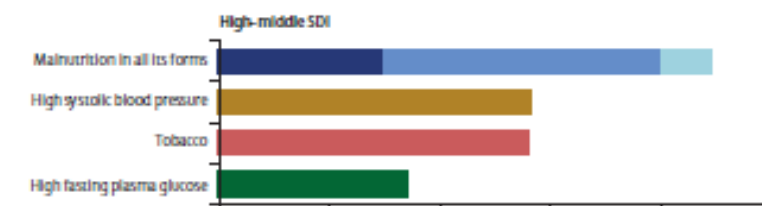
Global



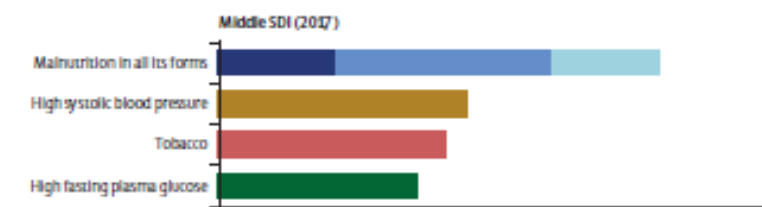
High



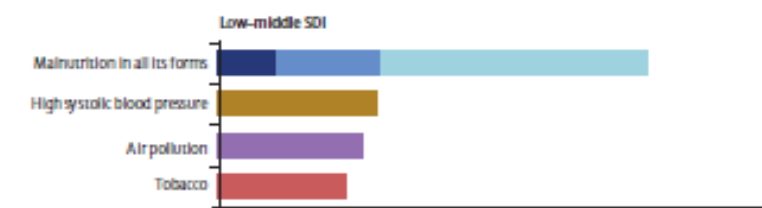
High-middle



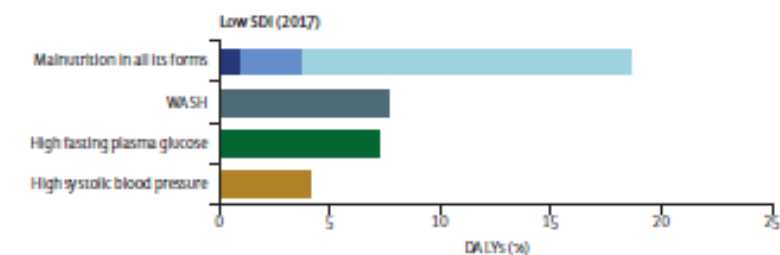
Middle



Low-middle

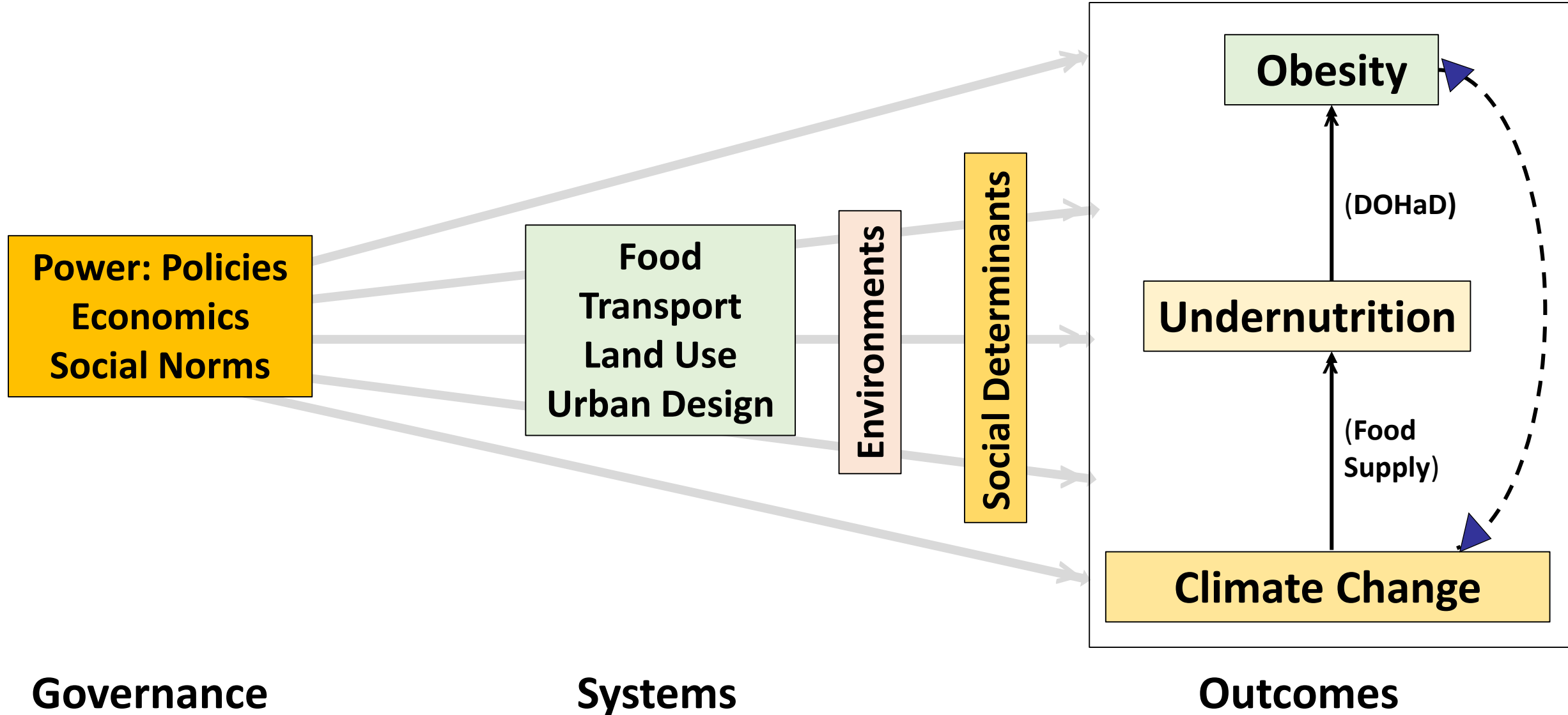


Low



LCO Framework

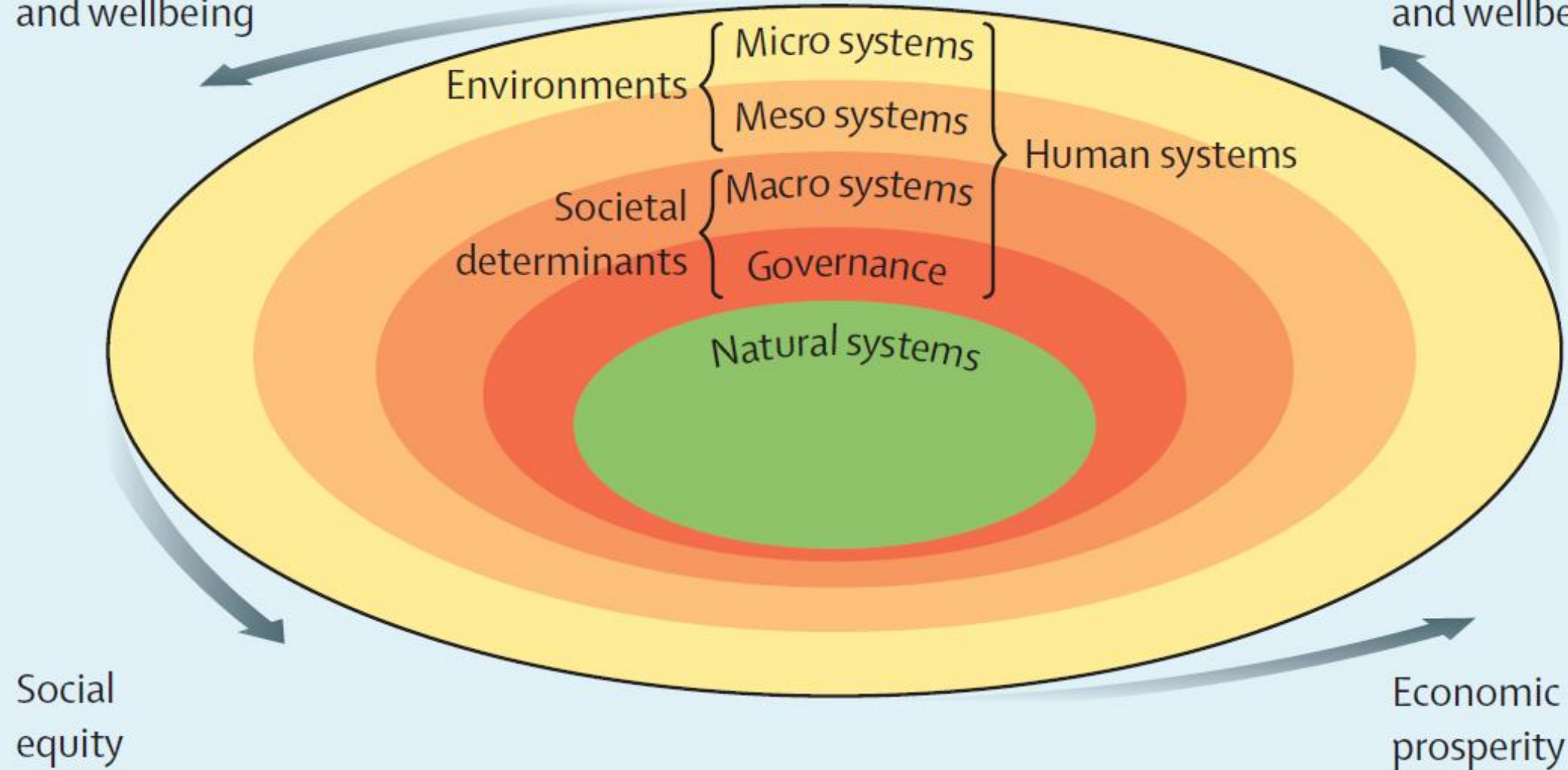
The Global Syndemic



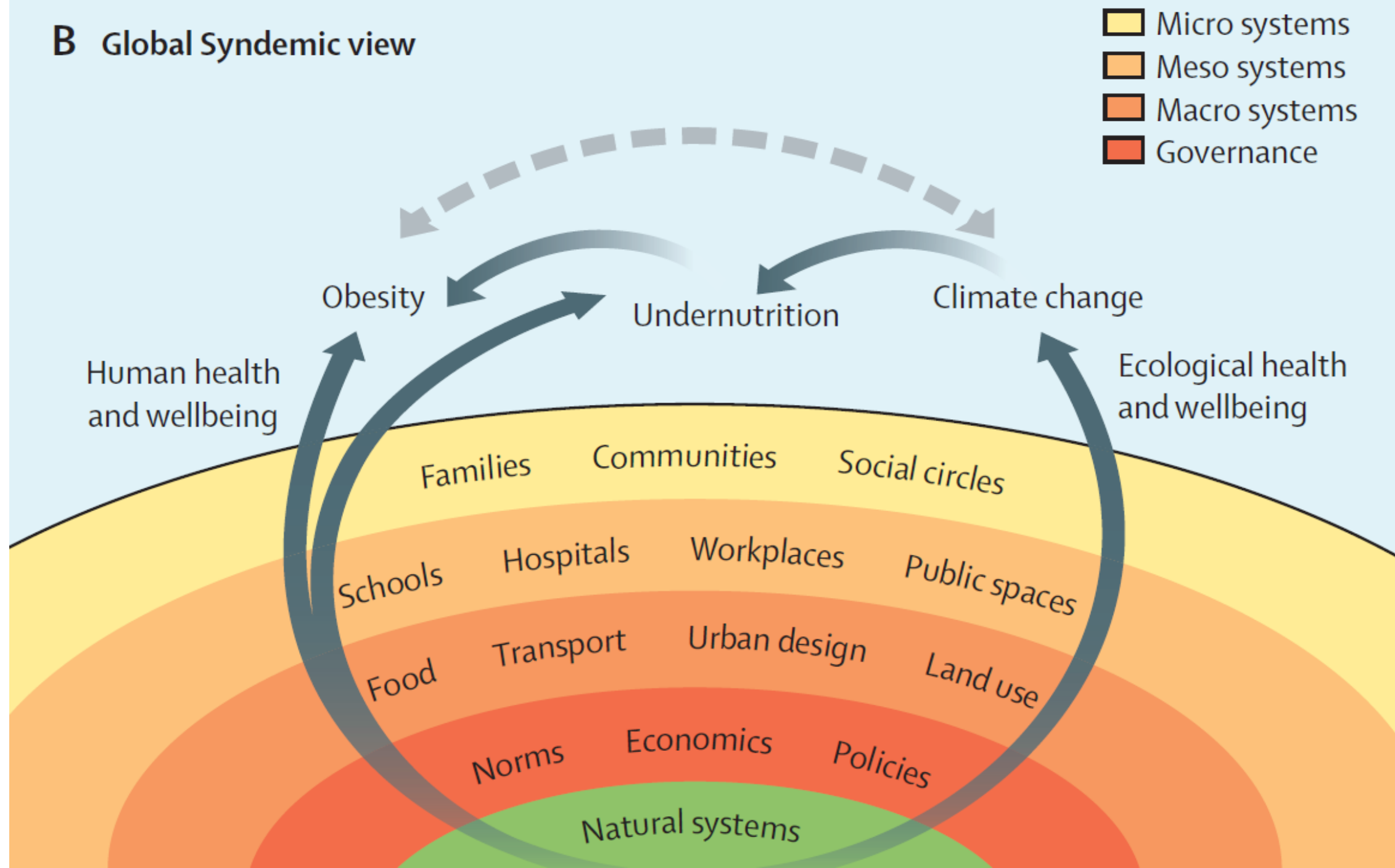
A Global outcomes view

Human health
and wellbeing

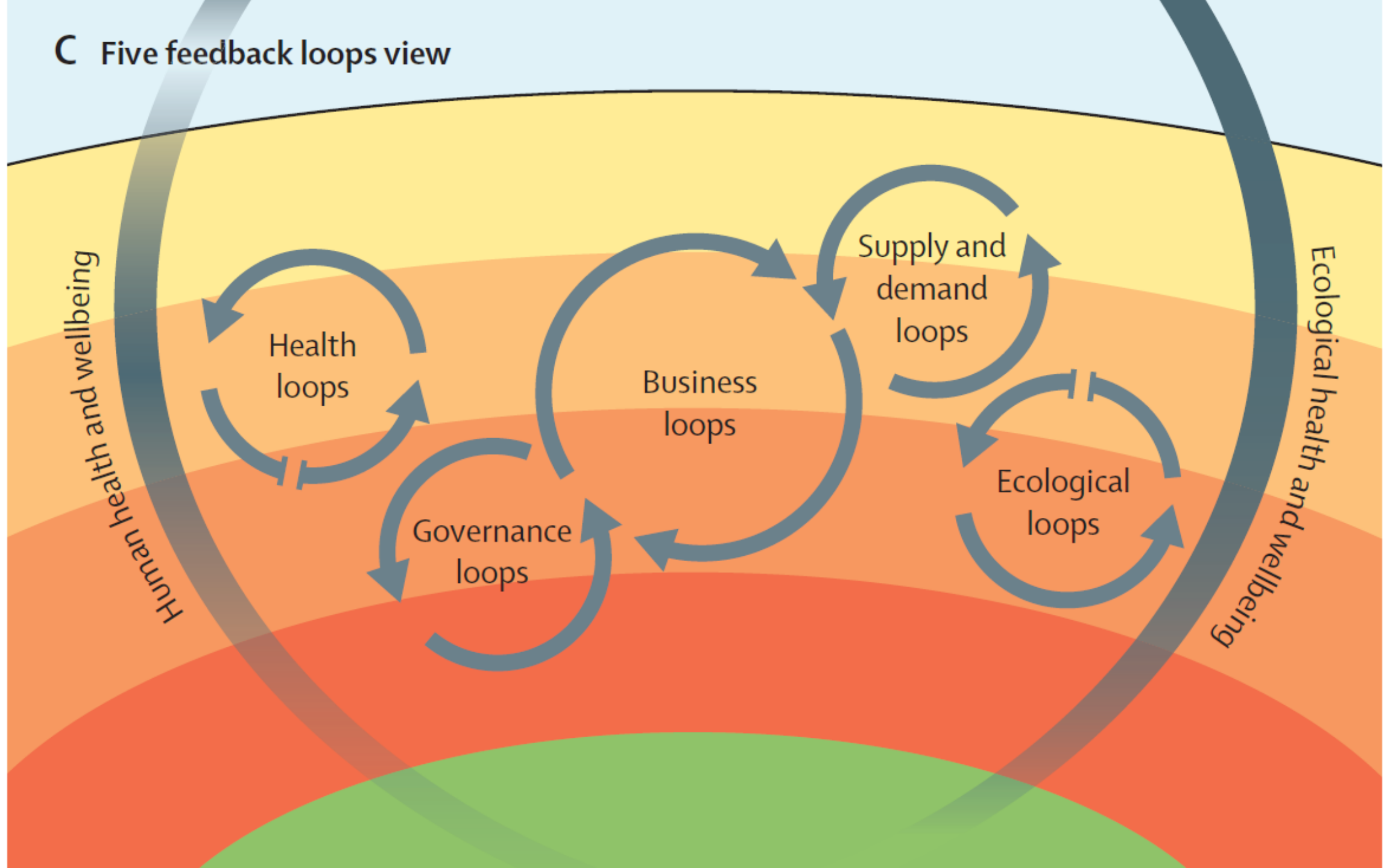
Ecological health
and wellbeing



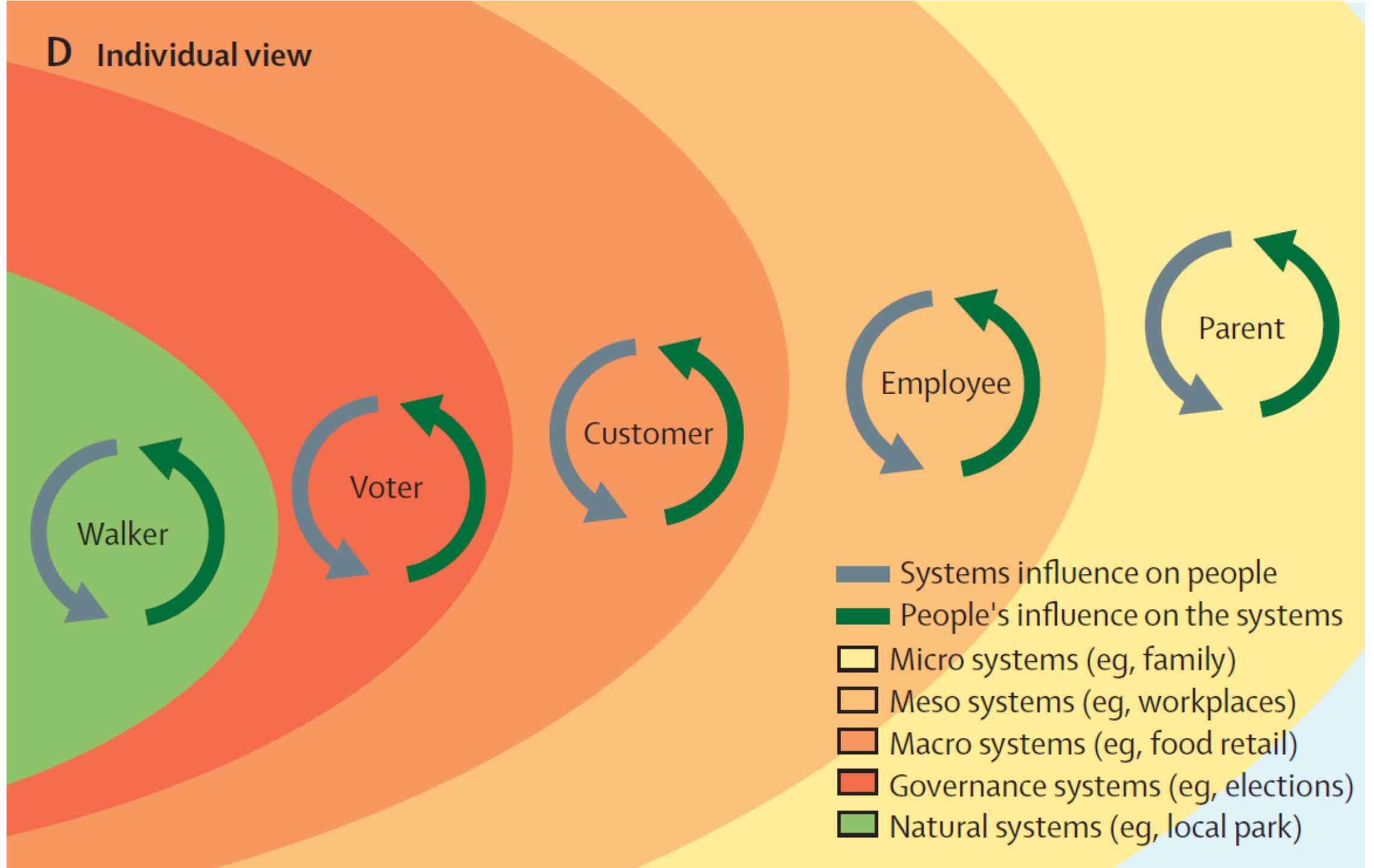
B Global Syndemic view



C Five feedback loops view



D Individual view



Summary

➤ *The Global Syndemic*

- *Common drivers for obesity, undernutrition, climate change*
- *Common solutions – double and triple duty actions*

➤ *Systems underpin the syndemic and its outcomes*

- *Ecological health, Human health, Social equity, Economic prosperity*

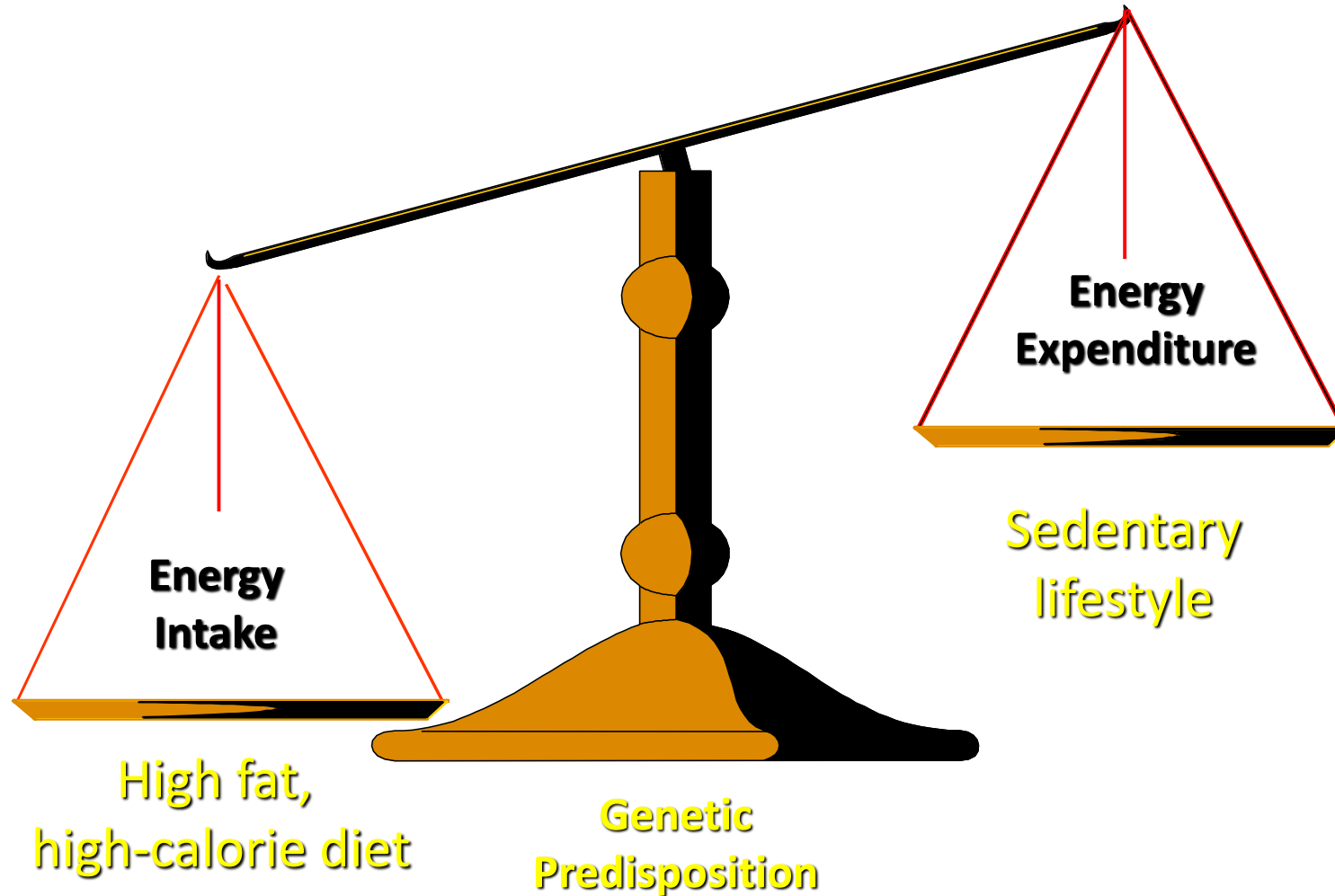
➤ *Five feedback loops*

- *Governance, Business, Supply/Demand, Health, Ecological*

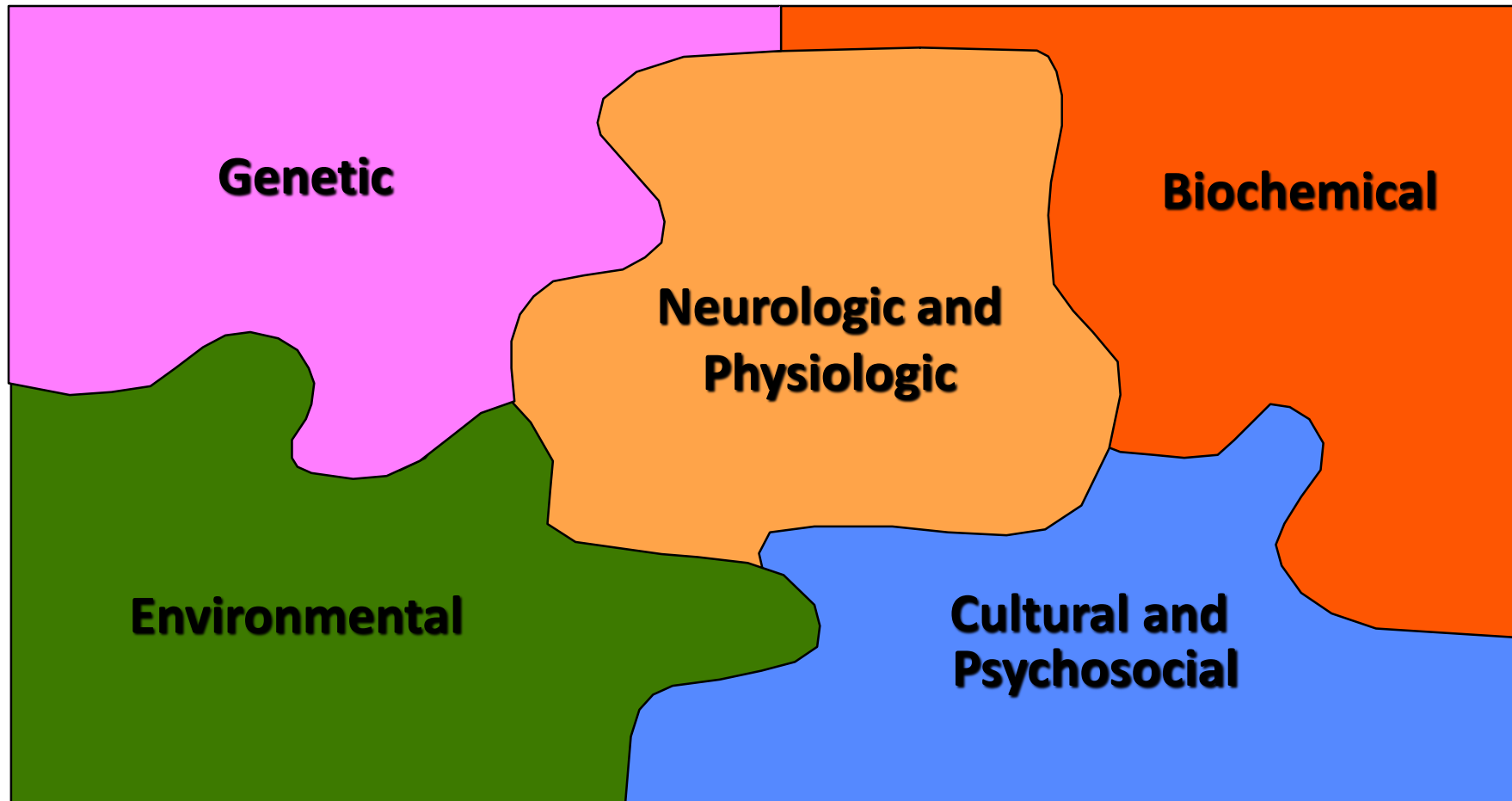
➤ *Individuals*

- *Affected by the systems and agents within the systems*

Etiology of Obesity



*Aetiology of Obesity:
Numerous Complex and Interrelated Factors*



Obesity Overview

The World Health Organization, (WHO) has identified Obesity as one of the greatest public health challenges of the 21st century. Overweight and obesity are now linked to more deaths worldwide than underweight..

Obesity is fast becoming the a leading health concern in the US, with the following statistics

39.8 % of adults
> 20 years of age with Obesity

70.7 % of adults
with Overweight and Obesity

Obesity Rises



Healthcare
Cost Rises



Obesity significantly increases a person's risk of developing numerous non-communicable diseases, including cardiovascular disease, cancer, diabetes, sleep disturbance, and other disabilities. The risk of developing more than one of these diseases also increases with excess body weight.

Why Obesity IS a disease

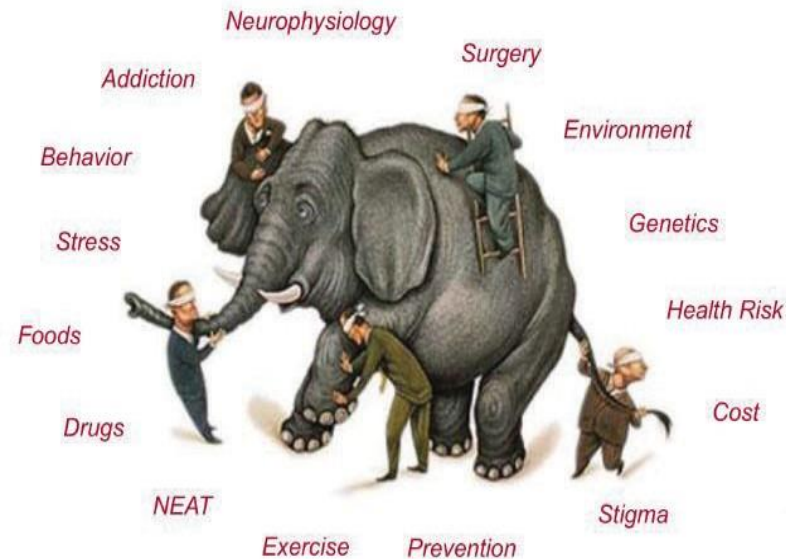
It is associated with **impaired body function**

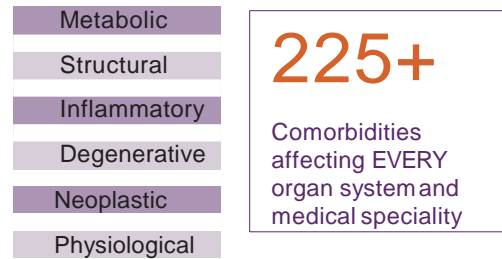
Like other diseases, it results from **physiological dysfunction**

Though frequently precipitated by environmental forces in modern society, the final common pathway of obesity reflects abnormal physiology

It causes, exacerbates or **accelerated more than 225** comorbid diseases

It is associated with a substantial burden of morbidity and **premature death**





It is evident from multiple population studies that obesity, that an increase in adipose tissue or excess fat- leads to dysfunctional fat tissue resulting in hormonal (endocrine) and immune dysfunction- called Adiposipathy or **SICK FAT DISEASE**. It also results in pathogenic physical forces from excess body fat causing stress and damage to other body tissues, called **Adiposity or Fat Mass Disease**.

As the obesity epidemic soars, it is important to note that most doctors do not have the clinical training to appropriately treat it.

It is imperative to seek out a physician specifically trained in Obesity Medicine and certified by the American Board of Obesity Medicine, which is a specialty dedicated to the comprehensive care of patients with overweight and obesity.



Classification of Obesity

Obesity can be classified into *three stages I, II, and III*. This Classification is determined by a combination of BMI(Body Mass Index) Body Fat Percentage, and Waist Circumference.

BMI

The following BMI chart is measured in kilograms per meters squared (kg/m²)

NORMAL WEIGHT	OVER-WEIGHT	CLASS I OBESITY	CLASS II OBESITY	CLASS III OBE-SITY
18.5-24.9	25.0-29.9	30.0-34.9	35.0-39.9	ε 40

Exceptions and Ethnic Variations for BMI

Different BMI cutoff points are more appropriate based upon ethnicity

ETHNICITY/ GEOGRAPH Y	OVERWEIGHT	OBESITY
CHINA	23-24	>27-29
JAPAN	>24	>29
INDIA	>23	>27
SINGAPORE	>22	>27
LATIN AMERICA, CENTRAL & SOUTH AMERICAN	>23	>27

Body Fat Pecrentage

Men >25 % Body Fat is Considered Obese
Women > 32 % Body Fat is Considered Obese

ESSENTIAL FAT	ATHLETES	FITNESS	ACCEPTABLE	OBESITY
Women: 10-13% Men:2-5%	Women: 14-20% Men: 6-13%	Women: 21-24% Men: 14-17%	Women: 25-31% Men: 18-24%	Women: ε 32% Men: ε 25%

How is Obesity Assessed?

- BMI
- Weight
 - Weight in earlier life
 - Adult weight gain
- Waist circumference; WHR
- Skin folds
- Body fat (DXA, BIA)
- Intramuscular fat (CT scan)

Waist Circumference/ Abdominal Obesity

Men \leq 40 Inches or 102 Centimeters

Women \leq 35 Inches or 88 Centimeters

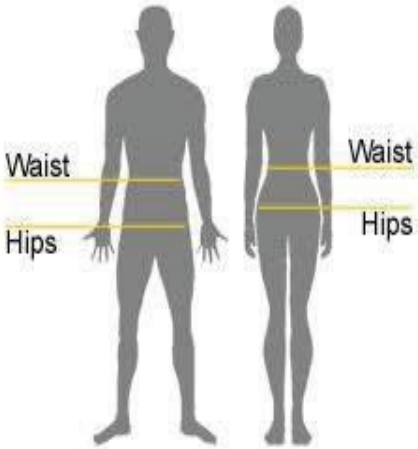
Abdominal Obesity cutoff points also vary based upon ethnicity

Abdominal Obesity in Men	Abdominal Obesity in Women
USA/Canada/Europe \leq 40 inches or 102cm	USA/Canada/Europe \leq 35 inches or 88 cm
Middle East/Mediterranean Sub-Saharan Africa \leq 37 inches or 94 cm	Middle East/Mediterranean Sub-Saharan Africa \leq 31.5 inches or 80 cm
South Asians, Chinese, Japanese South & Central American \leq 35 inches or 90 cm	South Asians, Chinese, Japanese South & Central American \leq 31.5 inches or 80 cm

Waist to Hip Ratio (WHR)

Men >1.1

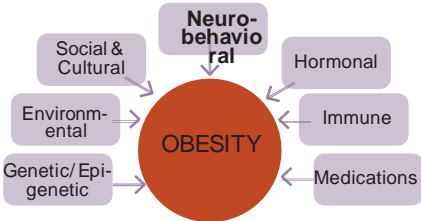
Women >0.8



Obesity Is	Obesity is Not
<ul style="list-style-type: none"> A disease A worldwide health concern Caused by many factors Treatable and manageable 	<ul style="list-style-type: none"> Your fault Yours to manage alone Just about food Cured by a miracle treatment

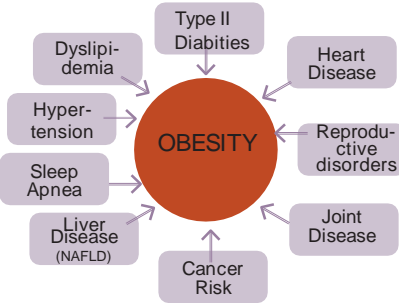
The causes of obesity are much more than simply overeating. It is a common misconception that obesity is due to lack of willpower or self-motivation. It is a chronic disease that needs to be prevented and managed, often requiring lifelong treatment. The causes of obesity are widespread and multifactorial.

Obesity can be caused by any one or a combination of the factors listed below:



Genetic

Obesity and Increased Risk of Chronic Metabolic Conditions.



Obesity Related Complications

Cardiometabolic Diseases	Biomechanical Diseases	Other
Dyslipidemia Pre-DM DM HTN CVD Stroke NAFLD/NASH Metabolic Syndrome	Stress incontinence Sleep apnea Hypoventilation syndrome Hernias Osteoarthritis Chronic pain DVT/blood clots Venous stasis	GERD Nephrolithiasis Cholelithiasis Skin disorders Infertility Depression Cancer Gout Dysomnia Disordered eating Surgical treatments and complications

Health Benefits of Treating Obesity

Even a moderate amount of weight loss can have significant health benefits.

CONDITION	AMOUNT OF WEIGHT LOSS NEEDED TO EFFECT IMPROVEMENT
TYPE 2 DIABETES	5-15% weight loss associated with lower A1C and reduce number and doses of medications
PREDIABETES & METABOLIC SYNDROME	10% weight loss to prevent type 2 Diabetes
DYSLIPIDEMIA	
HYPERTENSION	5-15% lowers systolic and diastolic blood pressure, reduces number and doses of antihypertensive medication
OBSTRUCTIVE SLEEP APNEA	10% weight loss required for significant improvement
KNEE PAIN AND FUNCTION	5-10% improves knee functionality, speed of walking
NON-ALCOHOLIC FATTY LIVER DISEASE	10-15% required for significant improvement
ASTHMA	7-8% required for significant improvement
PCOS	5% weight loss improves ovulatory cycles and subsequent pregnancy
MOBILITY, MORTALITY, QUALITY OF LIFE, DEPRESSION, URINARY INCONTINENCE, SEXUAL FUNCTION	5-15% may show significant improvement

Health Benefits of Treating Obesity

Even a moderate amount of weight loss can have significant health benefits.



Treatment of Obesity as a Chronic Metabolic Disease

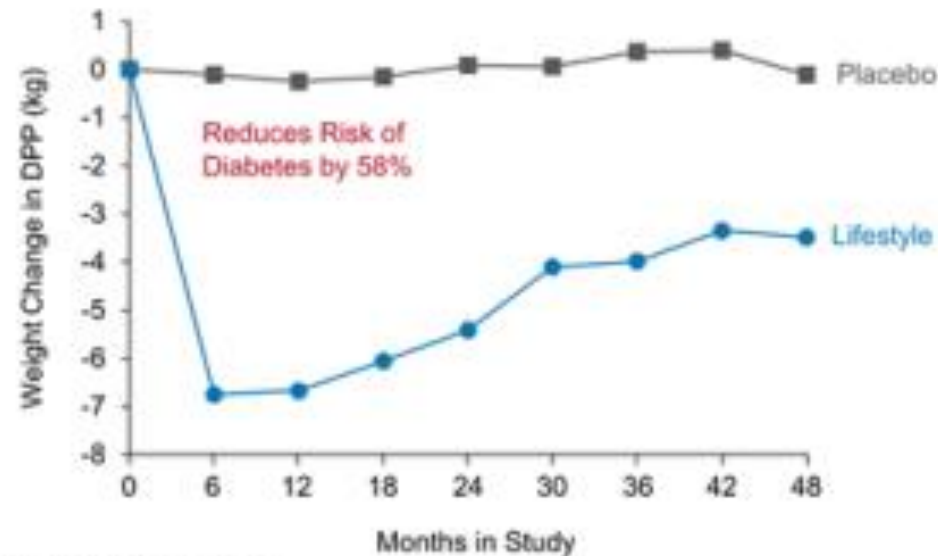
- Treat Obesity as any other disease
- Approach in a confident, supportive and non-judgemental way
- Listen and Hear what the patient is telling
- Pursue a step-wise strategy while exploring combinations as needed
- A comprehensive treatment approach with compassion is paramount

Treatment Goals

- Prevent further weight gain (minimum goal)
- Reduce body weight.
- Maintain lower body weight in the long term

Practical Solution is: 5-10 % weight reduction

Small Weight Loss Reduces Risk of Diabetes in the DPP



DPP, Diabetes Prevention Program.
Knowler WC et al. *N Engl J Med*. 2002;346(6):393-403.

Strategies for treatment of obesity

- **Diet**
- **Exercise**
- **Behavior therapy**
- **Medications**
- **Surgery**

Medications

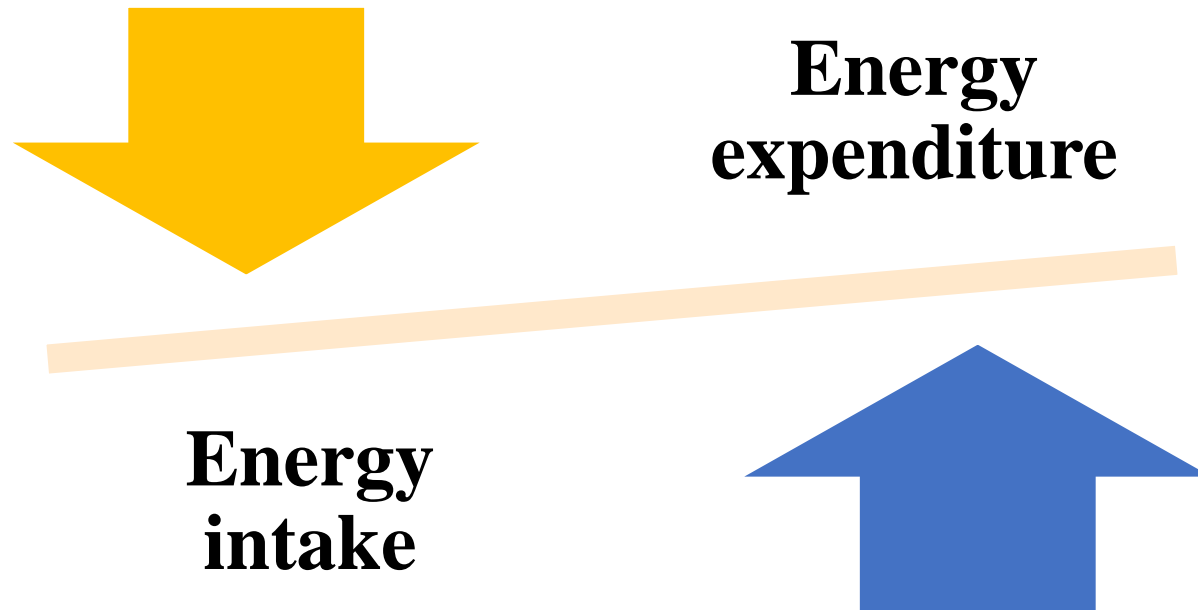
- All medications inherently have more risks than do diet and exercise
- *Medications should only be used for people in whom the benefit justifies the risk.*
- Since the introduction of Thyroid hormone to treat obesity in 1893, almost every drug in this respect, has caused undesirable outcomes
- *Obesity is a chronic disease.*
- Treatment is aimed at palliation.

Goals of therapy

- The ideal outcome is a return to normal body weight, but this is unrealistic.
- *Effective therapy:*
 - Weight loss > 2 kg during the 1st month
 - Weight loss > 5% below baseline by 3 to 6 months
 - Remain at this level
- *Weight loss of 10 – 15 % : very good response*
- Weight loss > 15% : Excellent response

Medications

- For weight loss, the obese patient must go into negative energy balance



Medications

1

- **Those that act primarily on the CNS to reduce food intake**

2

Drugs approved by the FDA for treatment of obesity

- *Approved for long-term treatment*
 - Orlistate
 - Sibutramine
- *Approved for short-term treatment*
 - Benzphetamine
 - Diethylpropion
 - Phendimetrazine
 - Phentermine

Drugs that are not generally approved to treat obesity

- Fluoxetine and Sertraline
- Bupropion
- Topiramate
- Zonisamide
- Lamotrigine
- Metformin
- Pramlintide
- Exenatide

Many anti-obesity drugs have been withdrawn because of poor efficacy and/or severe side effects :

- **Amphetamines** : high risk of dependence
- **Fenfluramine** : in 1997 risk of pulmonary hypertension and valvular heart disease
- **β 3 adrenergic agonists** : poor efficacy and sympathetic side effects
- **Thyroxine** : adverse effects including cardiac arrhythmias.
- **Rimonabant** : in 2008, risk of depression, psychosis
- **Sibutramine** : in 2010 due to cardiovascular safety concerns

Anti-obesity Drugs :

Topiramate

- Is approved as an antiepileptic and anti-migraine
- *In clinical studies, its use was associated with weight loss*
- It is a weak carbonic anhydrase inhibitor
- It modulates the effects at receptors for GABA receptor (*one potential mechanism to reduce food intake*)
- Also exhibits state-dependent blockade of voltage-dependent Na⁺ or Ca²⁺ channels.

Indications for pharmacotherapy in obesity

- ***Clinically significant obesity:***
 - BMI 30 kg/m², or
 - BMI 25 kg/m² with 1 obesity-related co-morbidity
- ***Failure of adequate trial (3–6 months) of lifestyle and dietary modifications***
 - Weight loss <1 kg/month, No specific contradictions

Practical Approach to Obesity Treatment

BMI	RISK RATING	LIFE STYLE	OBESITY DRUG	SURGERY
25 – 30	Low	Use		
	High	Use	Consider	
30 – 35	Low	Use	Use	
	High	Use	Use	
35 – 40	Low	Use	Use	
	High	Use	Use	Consider
> 40	High	Use	Use	Consider

RISK FACTORS : DM , HTN , CAD , Dyslipidemia , OSA

Type of cancer	Relative risk* with BMI of 25–30 kg/m ²	Relative risk* with BMI of ≥ 30 kg/m ²	PAF (%) for US population [‡]	PAF (%) for EU population [§]
Colorectal (men)	1.5	2.0	35.4	27.5
Colorectal (women)	1.2	1.5	20.8	14.2
Female breast (postmenopausal)	1.3	1.5	22.6	16.7
Endometrial	2.0	3.5	56.8	45.2
Kidney (renal-cell)	1.5	2.5	42.5	31.1
Oesophageal (adenocarcinoma)	2.0	3.0	52.4	42.7
Pancreatic	1.3	1.7	26.9	19.3
Liver	ND	1.5–4.0	ND	ND
Gallbladder	1.5	2.0	35.5	27.1
Gastric cardia (adenocarcinoma)	1.5	2.0	35.5	27.1

Relative risks associated with overweight and obesity, and the percentage of cases attributable to overweight and obesity in the United States (US) and the European Union (EU). *Relative risk estimates are summarized from the literature cited in the main text. [‡]Data on prevalence of overweight and obesity are from the National Health and Nutrition Examination Survey (1999–2000)²⁰⁵ for men and women from the United States aged from 50–69 years. [§]Data on prevalence of overweight and obesity are from a range of sources²⁰⁶ for adult men and women residing in 15 European countries in the 1980s and 1990s. ^{||}PAFs were not estimated because the magnitude of the relative risks across studies are not sufficiently consistent. BMI, body mass index; ND, not determined; PAF, population attributable fraction (BOX 3).

Body Fatness, and the Risk of Cancer

BODY FATNESS, AND THE RISK OF CANCER

In the judgement of the Panel, the factors listed below modify the risk of cancer. Judgements are graded according to the strength of the evidence.

	DECREASES RISK		INCREASES RISK	
	Exposure	Cancer site	Exposure	Cancer site
Convincing			Body fatness	Oesophagus ¹ Pancreas Colorectum Breast (postmenopause) Endometrium Kidney
			Abdominal fatness	Colorectum
Probable	Body fatness	Breast (premenopause)	Body fatness Abdominal fatness	Gallbladder ² Pancreas Breast (postmenopause) Endometrium
			Adult weight gain	Breast (postmenopause)
Limited — suggestive			Body fatness Low body fatness	Liver Lung
Substantial effect on risk unlikely	None identified			

¹ For oesophageal adenocarcinomas only.

² Directly and indirectly, through the formation of gallstones.

Background

Table 3.1
Obesity-related cancers

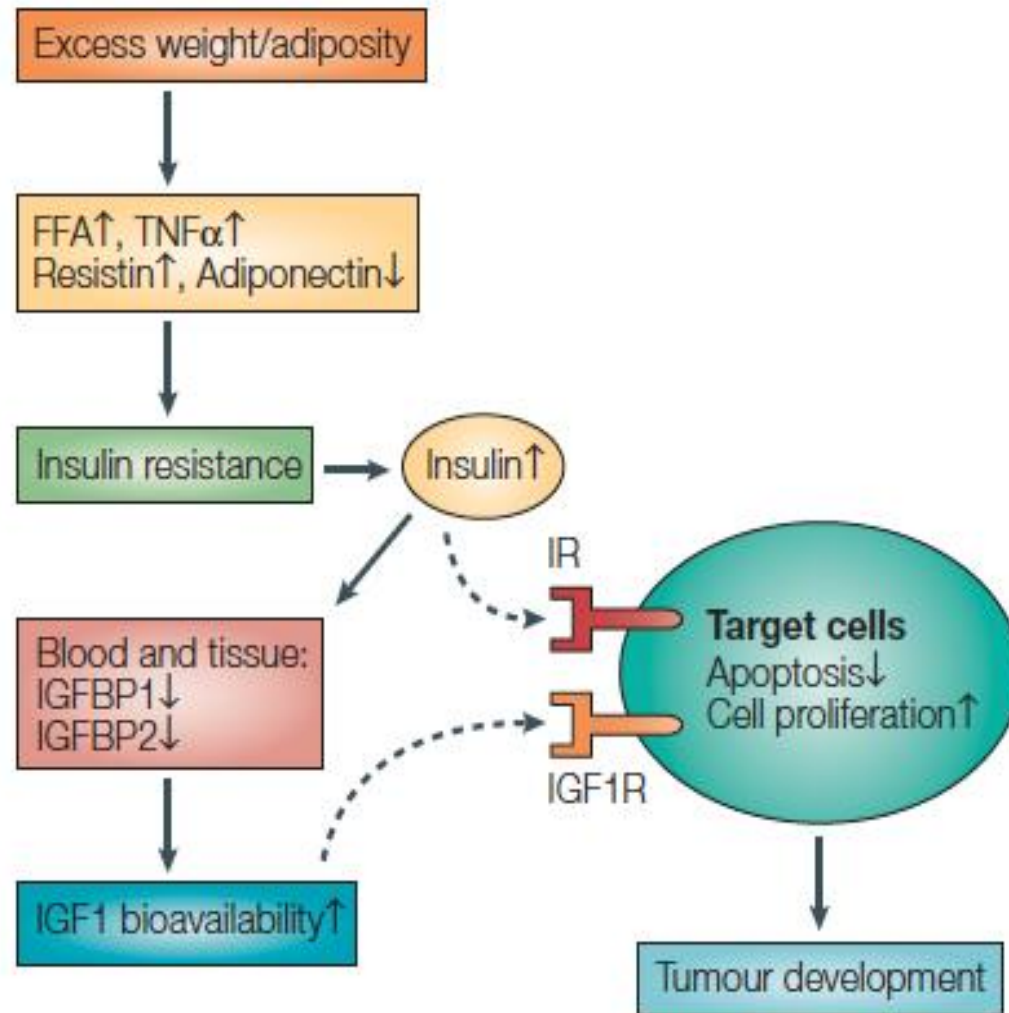
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Endometrial	2.0	3.5	56.8	45.2
Kidney (renal cell)	1.5	2.5	42.5	31.1
Esophageal (adenocarcinoma)	2.0	3.0	52.4	42.7
Pancreatic	1.3	1.7	26.9	19.3
Liver	ND	1.5–4.0	ND ^d	ND ^d
Gallbladder	1.5	2.0	35.5	27.1
Gastric cardia (adenocarcinoma)	1.5	2.0	35.5	27.1

Table 2 | **Associations of obesity with selected hormones and proteins**

Hormone or binding globulin	Obesity versus normal weight
Insulin	Increased levels with obesity
IGF1	Non-linear relation, with peak levels in people with BMIs of 24–27 kg/m ²
Free IGF1	Increased levels with obesity
IGFBP1	Decreased levels with obesity
IGFBP3	Increased levels with obesity or no observed effect
SHBG	Decreased levels with obesity
Total testosterone	Decreased levels with obesity (men); no observed effect (women); increased levels with obesity (premenopausal women with polycystic ovary syndrome)
Free testosterone	No observed effect or decreased levels with obesity (men); increased levels with obesity (women)
Total oestradiol	Increased levels with obesity (men and postmenopausal women); no observed effect (premenopausal women)
Free oestradiol	Increased levels with obesity (men and postmenopausal women); no observed effect (premenopausal women)
Progesterone	No observed effect or decreased levels with obesity in women with a susceptibility to develop ovarian hyperandrogenism (premenopausal women only)

BMI, body mass index; IGF1, insulin-like growth factor 1; IGFBP, IGF-binding protein; SHBP, sex-hormone-binding globulin.

Impact I



Candidate Mechanisms

- Insulin and insulin like growth factor axis
- Sex steroids
- Adipokines
- Obesity induced hypoxia
- Shared genetic susceptibility
- Migrating adipose stromal cells

High Insulin Levels are an adverse prognostic factor associated with:

- Breast cancer
- Colon cancer
- Prostate cancer

Sex Hormones

- *Higher rates of conversion of androgenic precursors to estradiol*
- *Increased aromatase activity through adipose tissue*
- *Data indicates that estrogen is both mitogenic and mutagenic*

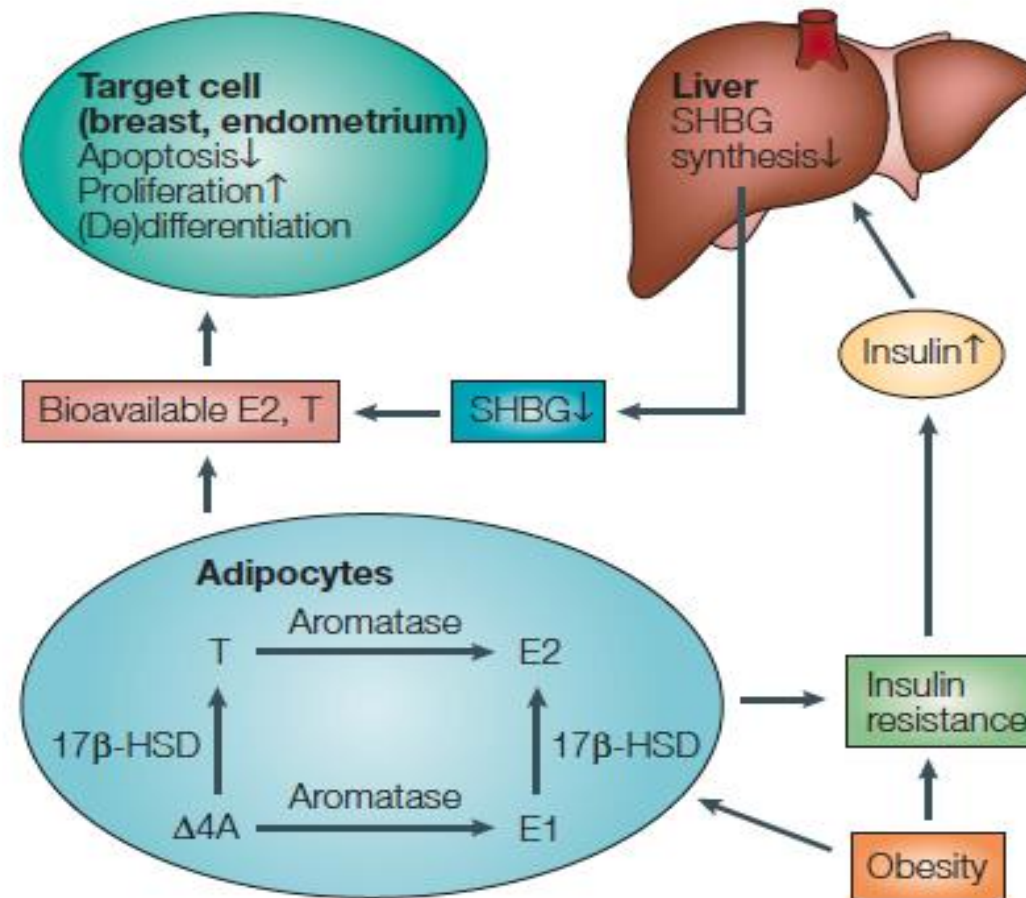
Endogenous Hormones and Breast Cancer Collaborative Group (EHBCCG)

- Nine prospective studies
- Risk of breast cancer increases at least two fold with increased levels of sex steroids
 - DHEA
 - DHEAS
 - Androstenedione
 - Estrone
 - Estradiol
 - Testosterone

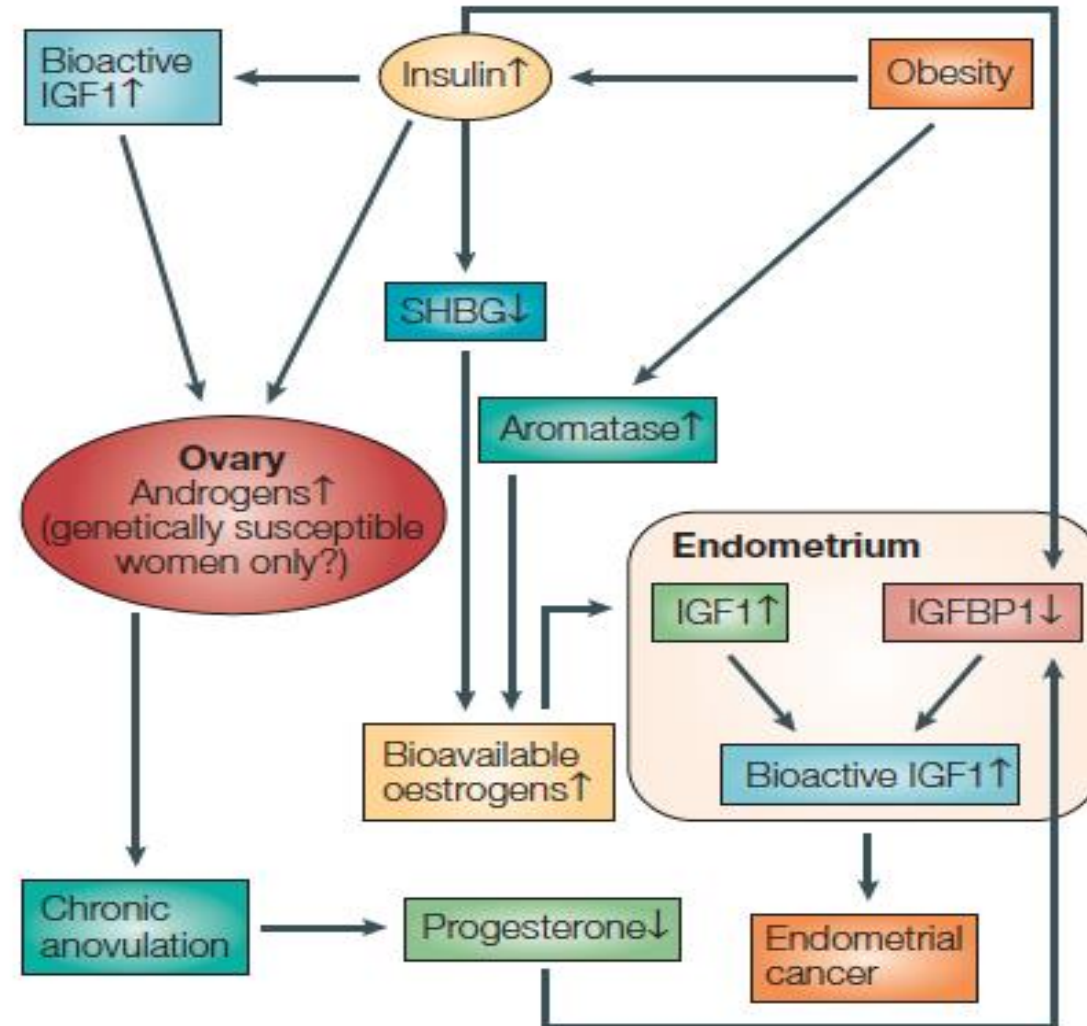
Estrogen stimulation in endometrial cancer

- Increases cellular proliferation
- Inhibits apoptosis
- Induces synthesis of IGF-1
- Progesterone induces synthesis of IGFBP-I which inhibits IGF-I

Effect of obesity on hormones



Obesity, Hormones and Endometrial Cancer



Leptin

- Leptin deficient mice overfeed and rapidly become hyperinsulinemic
- Long arm of leptin receptor (LRb) activates
 - PI3 kinase
 - MAPK
 - STAT (signal transduce and activator transcription)
 - C-fos

Adiponectin

- Most abundant adiponectine
- Important insulin sensitizing agent
- Inverse association of adiponectin concentrations and cancer
- Antiproliferative effects
 - ERK
 - ERK1
 - MAPK kinases
 - Induces p53 and Bax

Obesity Related Hypoxia

- Adipose tissue hypoxia is a key factor in the development of insulin resistance
- Regulation of chronic inflammation
- Reduced adiponectin
- Increased leptin
- High levels of tumor hypoxia correlate with high mortality
- HIF-1 alpha is associated with poor prognosis

Obesity related hypoxia

- White adipose tissue in obese mice is more hypoxic than in lean mice (15.2 mmHg versus 47.9 mmHg
 - Ye et al Am J Phys. Endo Met 2007
- Low oxygen concentrations have been associated with stimulation of melanocytes and development of melanoma
 - Through the AKT, ras/raf, PI-3-Kinase pathways
 - Bedogni Cancer Cell 2005

Shared Genetic Susceptibility

- Genome wide studies show at least 15 loci associated with obesity
- Cancer genome maps are derived from a number of parallel genome wide associated regions
- Overlap may exist for breast on 11p and 16q
 - Hofker et al Nat Genetic 2009

Obesity related inflammatory markers

- Increased C-reactive protein
- Activation of c-Jun NH2-terminal kinase
- Activation of I κ B kinase beta increases with adiposity
- Increased activated macrophage infiltration
 - Now recognized as a mechanism of insulin resistance

Mechanical Markers

- Hypertension
- Acid reflux
- Increased iodine uptake

Breast Cancer

- Increased postmenopausal breast cancer
- Decreased premenopausal cancer
- Increased weight gain 18-50 increases risk of breast cancer after menopause

Colon Cancer

- For men, increased BMI = increased risk
- The strongest association with abdominal obesity (waist circumference)
- Also, increased BMI is associated with rectal cancer

Esophageal Cancer

- Esophageal adenocarcinoma is 2X's higher in those who are overweight and obese
- Associated link with gastroesophageal reflux and Barrett's esophagus
- Obesity exacerbates esophageal inflammation

Prostate Cancer

- Pooled data: obesity is associated with a slight increased risk
- Obese men have more aggressive cancers
- Linked to hormone and growth factors (esp IGF-1)

Other Cancers

- Obesity is associated with renal cell cancer
 - Related to high insulin levels
- Associated with thyroid cancer
 - Mechanism is unknown
- Associated with gallbladder cancer
 - Possible mechanism related to frequency of gallstones

*So what do we know thus far
related to GYN cancers?*

- Obesity is **NOT** clearly associated with:
 - Vaginal cancer
 - Vulvar cancer
- Obesity is **possibly** associated with:
 - Cervical Cancer
 - Ovarian cancer -premenopausal

Obesity and Adult Weight Gain

- Strongly associated with *endometrial cancer*

Endometrial Cancer

- Most common gynecologic cancer
- We perceive it to be associated with obesity
- Increasing incidence
- Hormone related cancer

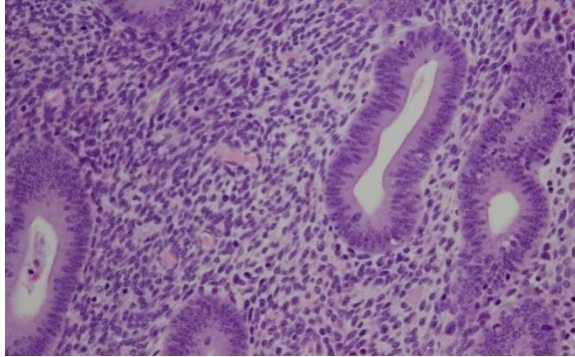
Obesity

- Strongest risk factor for endometrial cancer¹
 - RR 4.0 - BMI>32 kg/m²
 - RR 6.0 - BMI>35 kg/m²
- Elevated endogenous estrogens
- “Hyper-estrogenic” state does not account for all cases²
- Other obesity-related factors may contribute to increased risk for endometrial cancer

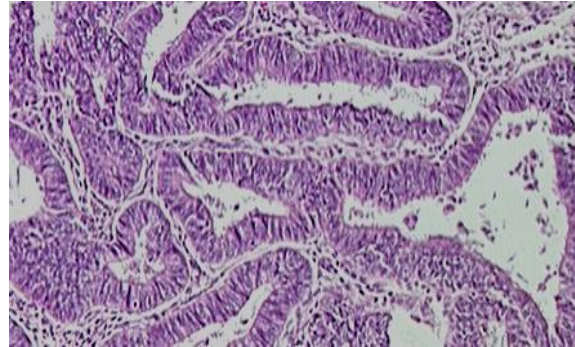
¹Brinton et al. Am J Obstet Gynecol 1992

²Potishman et al. JNCI 1996

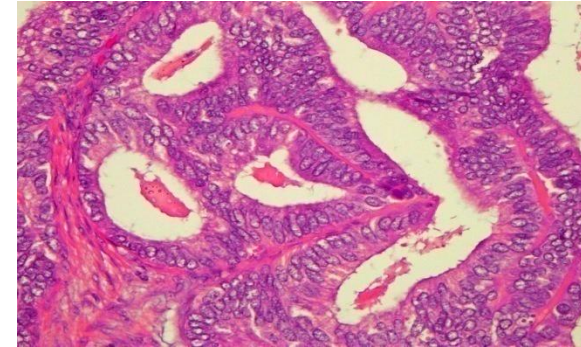
Progression of the Endometrium to Cancer



Normal



Complex atypical
hyperplasia (CAH)

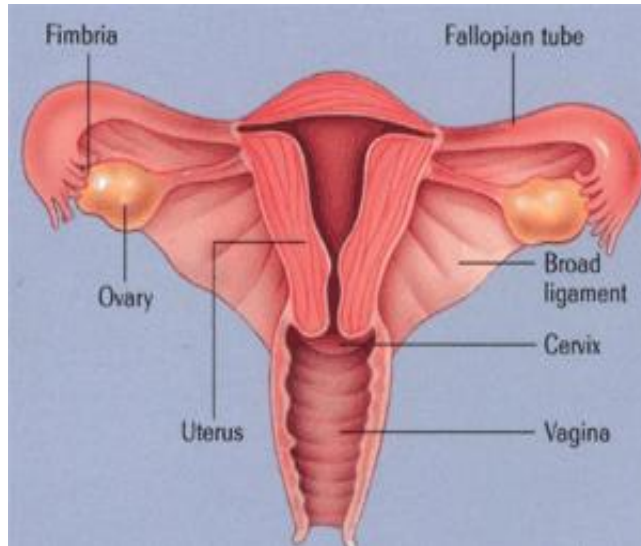


Grade 1
Endometrial
cancer

- 23% of complex atypical hyperplasia (CAH) progresses to endometrial cancer
- Excess of estrogen and lack of progesterone causes abnormal proliferative drive
- Subset of aggressive histologies that do not follow this progression pathway

Endometrial Cancer: Annual Incidence and Mortality

ACS Estimates



<u>Year</u>	<u>Cases</u>	<u>Deaths</u>
1987	35,000	2,900
2008	40,100	7,170*

***250% increase**

American Cancer Society 2008

Goal: *Prevention of deaths*

40,000+ cases

7,000+ deaths

34,000	endometrioid	3,710
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28,800	G1-2	1,820
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5,200	G 3	1,890
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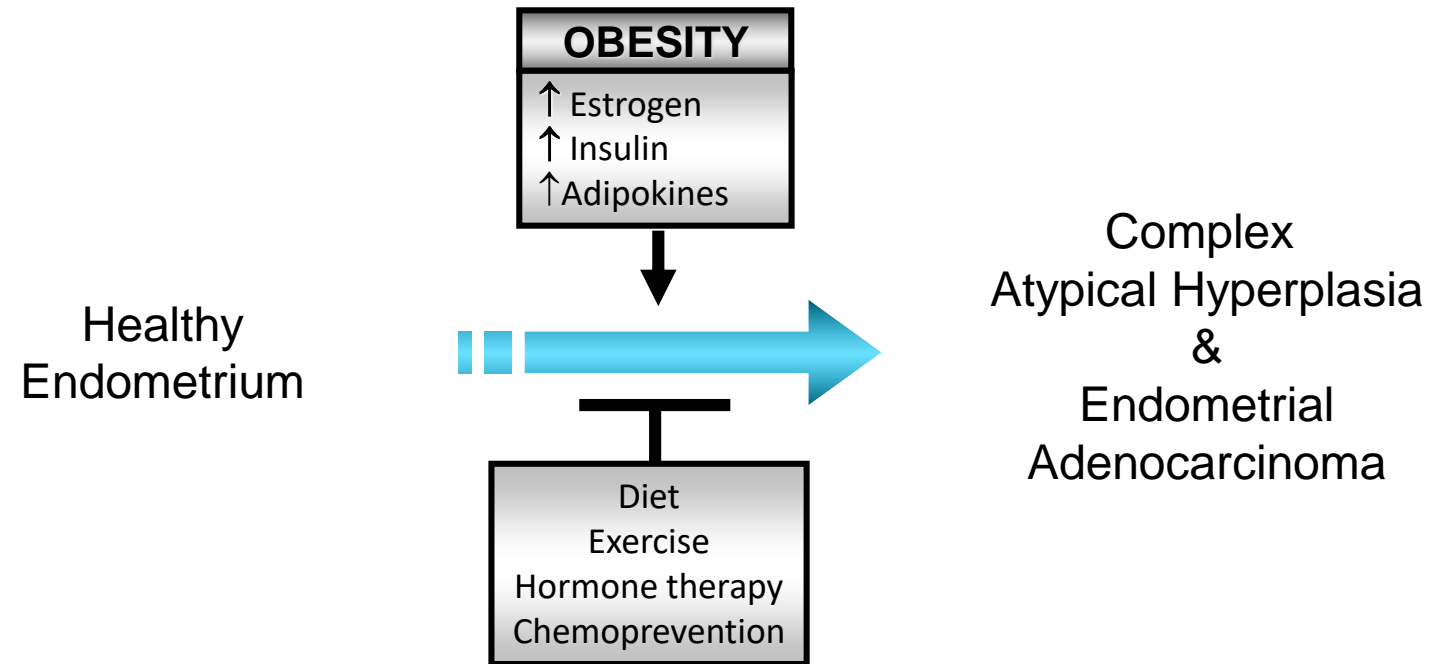
4,000	UPSC	2,800
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1,200	Clear Cell	560
-------	------------	-----

800	Sarcoma/CarcinoSarc	400
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How do
we
identify
these
patients
and
prevent
death?

Background



Prevention of Obesity-associated Endometrial cancer

- Oral contraceptives
- Progestins (including IUD w/Progestin)
- Weight loss
- Bariatric surgery
- ? Metformin

Association Between Adiponectin, Insulin Resistance, and Endometrial Cancer

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BACKGROUND: Obesity is a well known risk factor for the development of endometrial cancer; however, weight alone does not account for all cases. The authors hypothesized that insulin resistance also contributes to an increased risk for endometrial cancer. Adiponectin is a protein secreted by adipose cells and has been shown to be a surrogate marker for insulin resistance, with low levels of adiponectin correlated with hyperinsulinemia and degree of insulin resistance. The purpose of the current study was to determine whether there was an independent

METHODS: A case-control study was performed on 129 (cases) and 238 women with no history of cancer. Levels were measured using enzyme-linked immunosorbent assay for their association with endometrial cancer. Univ

RESULTS: The mean serum adiponectin levels were 88.8 ± 63.3 ng/mL than among controls (148.2 correlation continued to be observed after control diabetes, and hypertension. Cases were significant adiponectin levels in the lowest (odds ratio [OR] = 0.95; CI, 1.49-24.57 [*P* < .001]) and intermediate to 6.21 [*P* = .05]) when compared with controls.

CONCLUSIONS: Adiponectin level was found to be associated with endometrial cancer. Women with likely to have low adiponectin levels than controls mass index. This suggested that insulin resistance is endometrial cancer. *Cancer* 2006;106:2376-81. ©

KEYWORDS: adiponectin, endometrial cancer, insulin resistance, pregnancy.

Endometrial cancer is the most common and the fourth most common cancer among women in the United States. It is estimated that 40,880 new cases and 7311 cancer will have occurred during 2005.¹ Endometrial cancer far exceeds the mortality

Obesity is a well known risk factor for endometrial cancer, with the level of risk related to body mass index (BMI).² Women with a body mass index (BMI) ≥32 of 4.0 and women with a BMI ≥35 kg/m² when compared with women with a BMI <32 have elevated levels of endogenous estrogen and androstenedione to estrone in peripheral blood. Obesity is a well-known risk factor for endometrial cancer with the level of risk

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ONCOLOGY

Circulating adiponectin levels and risk of endometrial cancer: the prospective Nurses' Health Study

Pamela T. Soliman, MD, MPH; Xiaohui Cui, MD; Qian Zhang, PhD; Susan E. Hankinson, ScD; Karen H. Lu, MD

OBJECTIVE: Adiponectin, a protein secreted by adipose cells, is inversely associated with endometrial cancer. Our objective was to assess prediagnostic adiponectin levels in relation to risk of endometrial cancer.

STUDY DESIGN: This was a prospective nested case-control study within the Nurses' Health Study with 146 cases and 377 controls. Adiponectin was measured using enzyme-linked immunosorbent assay. Logistic regression analyses were performed adjusting for known endometrial cancer risk factors.

RESULTS: Mean age at diagnosis was 64.6 years. Mean interval between blood draw and diagnosis was 7.4 years (range, 2-13). There

was no difference in median adiponectin (cases 12.9 vs controls 12.9 μg/mL; *P* = .97). Adiponectin >15 μg/mL was not associated with endometrial cancer risk (relative risk = 0.86; 95% confidence interval, 0.53-1.39; *P* = .48), even among postmenopausal women (odds ratio, 0.66; 95% confidence interval, 0.29-1.5). Results did not vary by time from blood draw to diagnosis (*P* for heterogeneity = .18).

CONCLUSION: Prediagnostic adiponectin was not predictive of endometrial cancer risk. Further study will better define the relationship between adiponectin and endometrial cancer.

Key words: adiponectin, endometrial cancer, insulin resistance, obesity, risk factors

Cite this article as: Soliman PT, Cui X, Zhang Q, et al. Circulating adiponectin levels and risk of endometrial cancer: the prospective Nurses' Health Study. *Am J Obstet Gynecol* 2011;204:167.e1-5.

Endometrial cancer is the most common gynecologic malignancy and the fourth most common cancer among women in the United States. It is estimated that 43,470 new cases and 7950 deaths from endometrial cancer will have occurred during 2010.¹ Obesity is a well-known risk factor for endometrial cancer with the level of risk

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related to the degree of obesity. Women with a body mass index (BMI) ≥32 kg/m² have a relative risk of 4.0 and women with a BMI ≥35 kg/m² have a relative risk of 6.0 when compared to women with a BMI of <23 kg/m².² The relationship between obesity and endometrial cancer is complex and likely involves multiple pathways including the sex steroid, insulin, and inflammation pathways.³

Adipose tissue secretes a number of metabolically active cytokines and hormones including adiponectin, leptin, resistin, and tumor necrosis factor-α.⁴ Adiponectin, the most abundant adipokine, is secreted exclusively by adipocytes.^{5,6} Low levels of adiponectin have been shown to have a high correlation with hyperinsulinemia and the degree of insulin resistance independent of adiposity, suggesting that adiponectin level may serve as a surrogate marker for insulin resistance.⁷ Adiponectin levels have also been shown to be decreased in both obesity and type 2 diabetes, a disease generally considered an independent risk factor for endometrial cancer.⁷ In addition, adiponectin has a longer half-life than most polypeptide hormones,⁸ and circulating levels are not affected significantly by either fasting or oral intake.⁹

In a previous retrospective case-control study performed at M. D. Anderson Cancer Center, serum adiponectin level was independently associated with endometrial cancer, even after adjustment for other known risk factors such as BMI, age, diabetes, and hypertension.¹⁰ Several other authors have also evaluated the relationship between adiponectin levels and endometrial cancer and found a similar association.^{11,12} More recently, Cui et al¹³ published the first prospective assessment of prediagnostic adiponectin levels and risk of endometrial cancer. High circulating levels of adiponectin were associated with a significant decrease in risk of endometrial cancer independent of other obesity-related risk factors.

We conducted a case-control study nested within the prospective Nurses' Health Study (NHS) to assess if baseline circulating levels of adiponectin were associated with endometrial cancer risk, independent of other known risk factors including obesity, age, diabetes, and parity. We hypothesized that higher circulating adiponectin levels in healthy women would be independently and inversely associated with risk of endometrial cancer.

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Plasma Adiponectin Levels and Endometrial Cancer Risk in Pre- and Postmenopausal Women

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Background: Adiponectin, an adipocytokine secreted by adipose tissue, is decreased in obesity, insulin resistance, type 2 diabetes, and polycystic ovary syndrome, all of which are well-established risk factors for endometrial cancer.

Methods: We conducted a case-control study nested within the European Prospective Investigation into Cancer and Nutrition to examine the relation between prediagnostic plasma adiponectin levels and endometrial cancer risk. Among pre- and postmenopausal women who were not currently using exogenous hormones, 294 women developed incident endometrial cancer during an average of 5.1 yr of follow-up. Using risk set sampling, 548 control subjects were selected, matched on

center, age, menopausal status, phase of menstrual cycle, time of blood draw, and fasting status. Conditional logistic regression models were used to estimate relative risks and 95% confidence intervals.

Results: Adiponectin levels were inversely associated with endometrial cancer risk [body mass index-adjusted relative risk for the top vs. bottom quartile = 0.56 (95% confidence interval 0.36-0.86), *P*_{trend} = 0.006]. There was evidence of a stronger inverse association among obese women than among nonobese women (*P*_{interaction} = 0.03). The inverse association also appeared stronger for women who developed endometrial cancer during an average of 5.1 yr of follow-up than for women who developed endometrial cancer during an average of 5.1 yr of follow-up. The association remained statistically significant after separate adjustment for other obesity-related physiological risk factors such as C-peptide, IGF binding protein-1, IGF binding protein-2, SHBG, estrone, or free testosterone but only marginally statistically significant after simultaneous adjustment for these factors.

Conclusions: High circulating adiponectin levels are associated with reduced endometrial cancer risk, largely independent of other obesity-related risk factors. (*J Clin Endocrinol Metab* 92:1255-1263, 2007)

First Published Online October 24, 2006

Abbreviations: BMI, body mass index; CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HRT, hormone replacement therapy; IARC, International Agency for Research on Cancer; IGF, IGF binding protein; MET, metabolic equivalent; OC, oral contraceptive; RR, relative risk.

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ONCOLOGY

Prospective evaluation of insulin resistance among endometrial cancer patients

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OBJECTIVE: Obesity and estrogen are strong risk factors for endometrial cancer (EC). Whereas diabetes also increases the risk, little is known about related insulin resistance (IR). The purpose of this study was to determine the prevalence of IR in newly diagnosed EC patients.

STUDY DESIGN: EC patients from a large, metropolitan county were prospectively enrolled from 2005 to 2008. Fasting serum was analyzed for glucose and insulin. IR was defined as a history of diabetes or a quantitative insulin sensitivity check index (QUICKI) ($1/[\log \text{fasting insulin} + \log \text{fasting glucose}]$) value of less than 0.357.

RESULTS: Among 99 patients normal QUICKI was found in 31. This was significantly associated with lower socioeconomic status (P

CONCLUSION: IR was highly prevalent in addition to obesity may provide information in the future.

Key words: diabetes, endometrial cancer

Cite this article as: Burzawa JK, Schmeler KM, Soliman PT, et al. Prospective evaluation of insulin resistance among endometrial cancer patients. *Am J Obstet Gynecol* 2011;204:355.e1-7.

Endometrial cancer is the most common gynecologic malignancy and the fourth most common cancer overall in women in the United States, accounting for an estimated 43,470 new cancer diagnoses and 7950 cancer-related deaths in 2010.¹ Increased risk of endometrial cancer is attributed to reproductive conditions resulting in relative estrogen excess such as

early menarche, late menopause, nulliparity, and chronic anovulation.²⁻⁶ Endometrial cancer is also strongly associated with obesity. Although this association has been classically attributed to peripheral aromatization of androstenedione to estrone, some studies have suggested that this relationship is not entirely explained by unopposed estrogen.^{7,8}

From the Departments of Gynecologic Oncology (Drs Burzawa, Schmeler, Soliman, Meyer, Bevers, Ramondetta, Gershenson, Brown, and Lu), Epidemiology (Dr Chang) and Biostatistics (Ms Urbauer), The University of Texas M. D. Anderson Cancer Center; Gynecologic Oncology of Houston (Dr Pustilnik); the Department of Obstetrics and Gynecology, The University of Texas Medical School at Houston, Lyndon B. Johnson General Hospital (Dr Ramondetta), Houston, TX; the Department of Obstetrics and Gynecology, Baylor College of Medicine (Dr Anderson), Houston, TX; and the Division of Cancer Control and Population Sciences, University of Puerto Rico, San Juan, Puerto Rico (Dr Tortolero-Luna).

Presented as a poster at the 40th Annual Meeting on Women's Cancer of the Society of Gynecologic Oncologists, San Antonio, TX, Feb. 5-8, 2009, and as a discussion poster presentation at the Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, June 4-8, 2010.

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Insulin resistance (IR) is a metabolic state in which the body's cells do not respond properly to insulin, a hormone that helps regulate blood sugar levels. IR is a common condition that can lead to type 2 diabetes. It is often associated with obesity, particularly abdominal obesity, and is a major risk factor for cardiovascular disease. In the context of endometrial cancer, IR is being studied as a potential link between obesity and cancer risk.

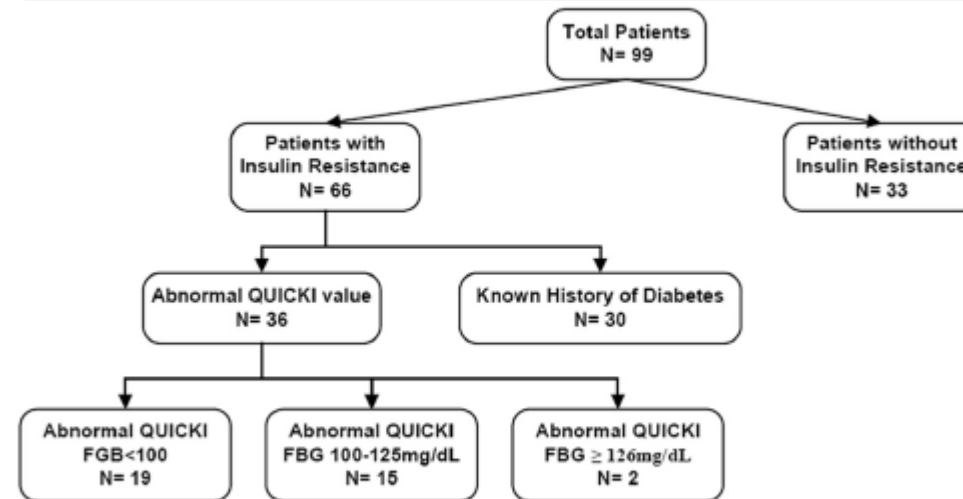
effect of estrogen on endometrial proliferation.¹³ Thus, IR may further clarify the link between obesity and endometrial cancer. We hypothesized that the risk of endometrial cancer associated with diabetes alone results in an underestimation of the true relationship between IR and endometrial cancer. We performed a geographically limited,

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FIGURE 1

CONSORT diagram of endometrial cancer patients by IR



A majority of patients had some form of IR, and more than half of these women had been previously undiagnosed. Severity of IR in these undiagnosed women ranged from abnormal QUICKI values to overt diabetes.

CONSORT, Consolidated Standards of Reporting Trials; IR, insulin resistance; QUICKI, quantitative insulin sensitivity check index.

Burzawa. Insulin resistance and endometrial cancer. *Am J Obstet Gynecol* 2011.

BASIC SCIENCE: GYNECOLOGY

Enhanced estrogen-induced proliferation in obese rat endometrium

Qian Zhang, PhD; Qi Shen, MD, PhD; Joseph Celestino; Michael R. Milam, MD; Shannon N. Westin, MD; Robin A. Lacour, MD; Larissa A. Meyer, MD; Gregory L. Shipley, PhD; Peter J. A. Davies, MD, PhD; Lei Deng, PhD; Adrienne S. McCampbell, PhD; Russell R. Broaddus, MD, PhD; Karen H. Lu, MD

OBJECTIVE: We tested the hypothesis that the proliferative estrogen effect on the endometrium is enhanced in obese vs lean animals.

STUDY DESIGN: Using Zucker fa/fa obese rats and lean control, we examined endometrial cell proliferation and the expression patterns of certain estrogen-regulated proliferative and antiproliferative genes after short-term treatment with estradiol.

RESULTS: No significant morphologic/histologic difference was seen between the obese rats and the lean rats. Estrogen-induced proliferative genes cyclin A and c-Myc messenger RNA expression were significantly higher in the endometrium of obese rats compared with

those of the lean control. Expression of the antiproliferative gene p27Kip1 was suppressed by estrogen treatment in both obese and lean rats; however, the decrease was more pronounced in obese rats. Estrogen more strongly induced the antiproliferative genes retinaldehyde dehydrogenases 2 and secreted frizzled-related protein 4 in lean rats but had little or no effect in obese rats.

CONCLUSION: Enhancement of estrogen-induced endometrial proliferative gene expression and suppression of antiproliferative gene expression was seen in the endometrium of obese vs lean animals.

Key words: endometrial, estrogen, obesity, proliferation

Cite this article as: Zhang Q, Shen Q, Celestino J, et al. Enhanced estrogen-induced proliferation in obese rat endometrium. Am J Obstet Gynecol 2009; 200:186.e1-186.e8.

Obesity affects more than 25% of adult women in the United States and continues to increase in prevalence. Numerous epidemiologic studies have demonstrated that obesity is a major risk factor for endometrial cancer.¹ Although an average woman has a 3% lifetime risk

of endometrial cancer, obese women have a 9-10% lifetime risk of endometrial cancer.² The increased peripheral conversion in adipose tissue of adrenal steroids to estrone and the increased bioavailability of free estrogens because of decreased sex hormone-binding globulin contribute to a "hyperestrogenic state" in obese women, which results in increased endometrial cell proliferation, leading to endometrial hyperplasia and cancer. Clinical studies have shown that patients with endometrial cancer exhibit higher plasma levels of estrogens vs controls.³ However, in a large study by Pottschman et al,⁴ the authors found that obesity remained a significant risk factor for the development of endometrial cancer even after controlling for endogenous estrogens. These results, and those of others, suggest that excessive estrogen alone cannot fully explain the association between obesity and endometrial cancer. Insulin resistance, associated with obesity, may enhance the effect of estrogen in the endometrium.⁵

Acting via its receptor, estrogen promotes cell proliferation through regulating the expression of a wide variety of

target genes. Studies by our group and others have shown that estrogen induces endometrial proliferative and antiproliferative gene expression.⁶ Among the estrogen-regulated genes, the expression of proliferative gene cyclin A and c-Myc are up-regulated by estrogen in the endometrium,^{6,7} and their expression is highly correlated with the entrance of cells into the S-phase,^{8,9} and linked to cellular proliferation or tumorigenesis.¹⁰ Expression of p27Kip1, a potent negative regulator of cell cycle and cellular proliferation, is inhibited by estrogen in the endometrial cell.¹¹ A progressive decrease in p27Kip1 expression from normal, through hyperplastic endometrium, to endometrial carcinoma has been reported.¹² Progesterone receptor (PR), secreted frizzled-related protein 4 (sFRP4), and retinaldehyde dehydrogenases 2 (RALDH2) are estrogen-regulated antiproliferative genes whose expression and activity are up-regulated by estrogen in the endometrium.¹³⁻¹⁶

In this study, we examined the effect of estrogen on endometrial cell proliferation in the Zucker fa/fa rats. The Zucker fa/fa rats exhibit many of the pathophys-

FIGURE 3

Expression of proliferative genes in the rat endometrium

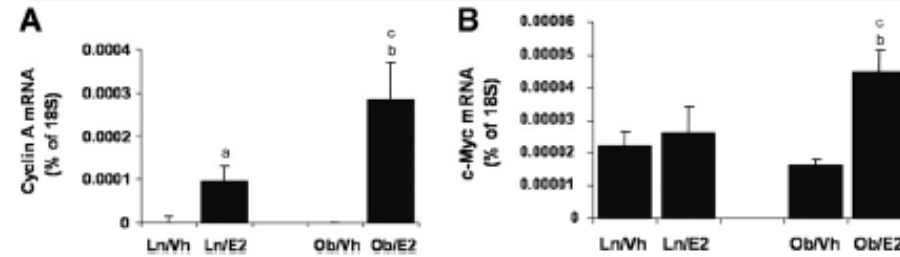
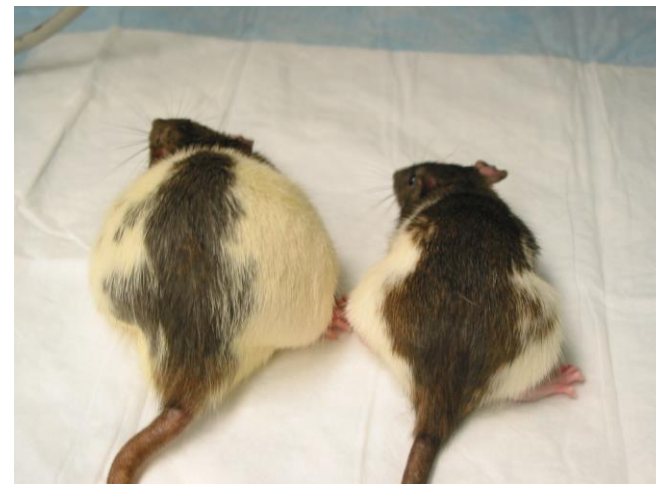
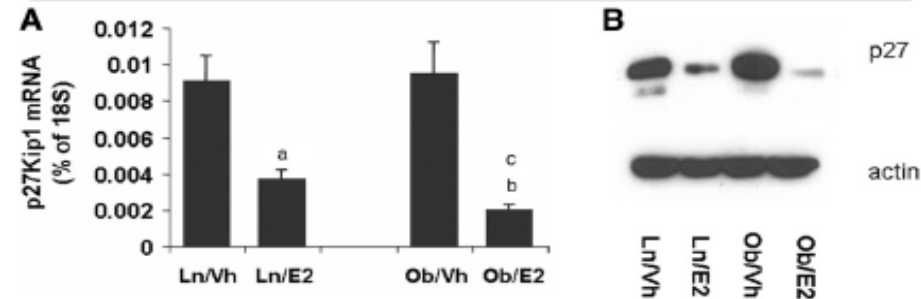


FIGURE 4

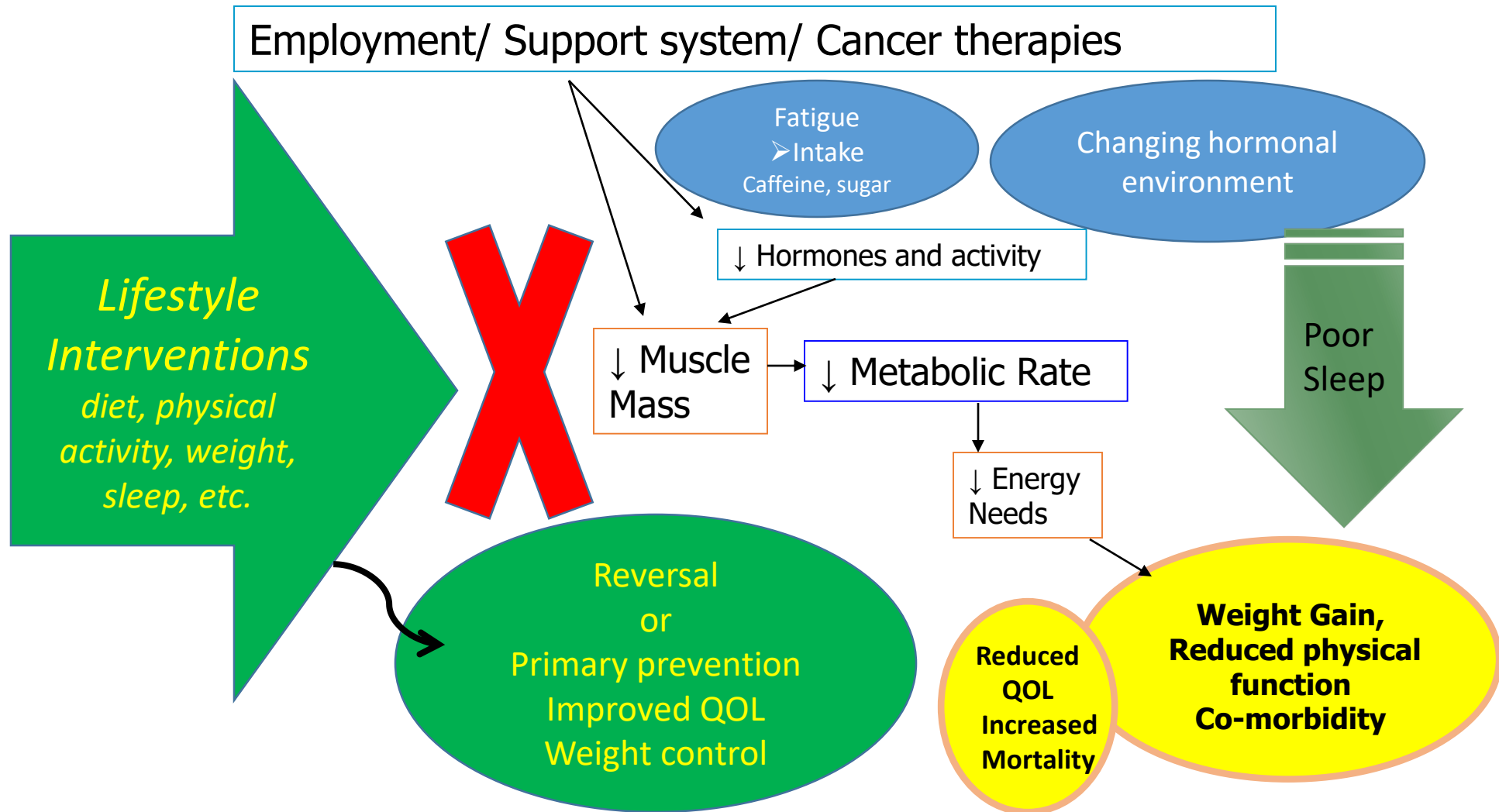
Expression of p27Kip1 in the rat endometrium



From the Departments of Gynecologic Oncology (Drs Zhang, Milam, Westin, Lacour, Meyer, and Lu and Mr Celestino) and Pathology (Drs Deng, McCampbell, and Broaddus), the University of Texas M. D. Anderson Cancer Center, and the Department of Pathology and Laboratory Medicine (Dr Shen), the Department of Integrative Biology and Pharmacology (Drs Shipley and Davies), the University of Texas Medical School at Houston, Houston, TX. Presented at the 99th Annual Meeting of the American Association for Cancer Research, San Diego, CA, April 12-16, 2008. Received March 18, 2008; revised June 4, 2008; accepted Aug. 30, 2008.

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Implications



Implications: Obesity- related Co-morbidity

- Cardiovascular
- Neurologic
- Psychiatric
- Pulmonary
- Vascular
- Gastrointestinal
- Genitourinary
- Metabolic
- Musculoskeletal

*Taking care of patients can be
extremely challenging...*

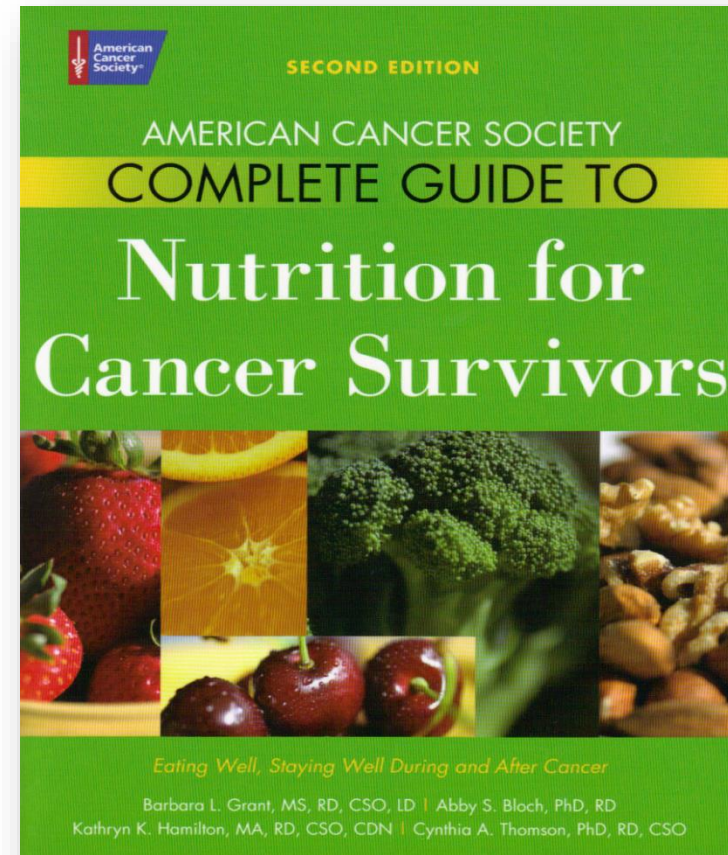
Opportunities

- Prevention of weight gain during adolescence and early adulthood
 - Weight trajectory “mapping”
- Monitor for central adiposity
 - Waist circumference
- Monitor for risk of obesity-related disease
 - Metabolic syndrome
- Intervene early if weight increases
- Do not under-estimate the role of regular, moderate physical activity

Therapy:

Don't wait, Don't hesitate

- Cancer diagnosis is an opportunity for behavior change
- Support systems are active
- Consequences (risk vs benefit) are high
- Engage healthcare team
- Small changes can translate to significant improvements in health indices and greater health and well-being



Summary

- *BMI associated with cancers*
- *Obesity is a complex system –no one size fits all*
- *Bariatrics (less obesity related cancers)*
- *Prevention methods include*
 - *Exercise*
 - *Weight loss*
 - *Diet control*

Questions?



THANKS!!!!