Psychiatry
UNIVERSITY OF TORONTO

Effects of Gender on Nutrient Intake and Brain Chemistry: Implications for Psychiatric Illness

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Disclosures

- Chair, Shire Canadian Advisory Board for Binge Eating Disorder
- Speaking on Binge Eating Disorder for Shire
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Eating Disorders as a Paradigm

Characteristics of an Eating Disorder:

1. **The presence of disturbed eating behavior**

2. **The presence of characteristic psychopathology**

Obesity per se is not an eating disorder but is best conceptualized as a complex, heterogeneous multi-determined metabolic disturbance. However, a significant percentage (35-40%) of obese subjects do have disturbed eating behavior and/or psychopathology (DSM 5 Binge Eating Disorder)

Anorexia Nervosa: DSM 5 Criteria

A. Restriction of energy intake relative to requirements leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health. Significantly low weight is defined as a weight that is less than minimally normal, or, for children and adolescents, less than that minimally expected.

B. Intense fear of gaining weight or becoming fat, or persistent behavior that interferes with weight gain, even though at a significantly low weight.

C. Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight.

Prevalence of Anorexia Nervosa

DSM 5 Criteria: 1.2 %

DSM IV Criteria 0.8 %

10% of cases are males; 10/1 ratio F/M

Why is this?

Bulimia Nervosa: DSM 5 Criteria

A. Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following:

(1) Eating, in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than most people would eat during a similar period of time under similar circumstances

(2) A sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating)\

Bulimia Nervosa: DSM 5 Criteria

B. Recurrent inappropriate compensatory behaviors in order to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, or other medications, fasting; or excessive exercise.

C. The binge eating and inappropriate compensatory behaviors both occur, on average, at least once per week for 3 months.

D. Self-evaluation is unduly influenced by body shape and weight.

E. The disturbance does not occur exclusively during episodes of Anorexia Nervosa

Prevalence of Bulimia Nervosa

DSM 5 Criteria : 2.4 %

DSM IV Criteria : 1. 8%

10 % of cases are male; 10/1 ratio F/M

Why is that ?

Binge Eating Disorder – DSM 5 Criteria

A. Recurrent episodes of binge eating, as defined previously
B. Marked distress regarding binge eating
C. The binge eating occurs at least once a week for 3 months.

D . The binge eating is not associated with the recurrent use of inappropriate compensatory behavior and does not occur exclusively during the course Bulimia Nervosa or Anorexia Nervosa.

Binge Eating Disorder

Epidemiology:

- BED is more common than the other major eating disorders anorexia nervosa or bulimia nervosa
- Lifetime prevalence of ~3% among women; 2% among men in US
- 65% female, 35% male : 2/1 ratio F/M
- Less preponderance of females/males in BED compared to AN and BN.

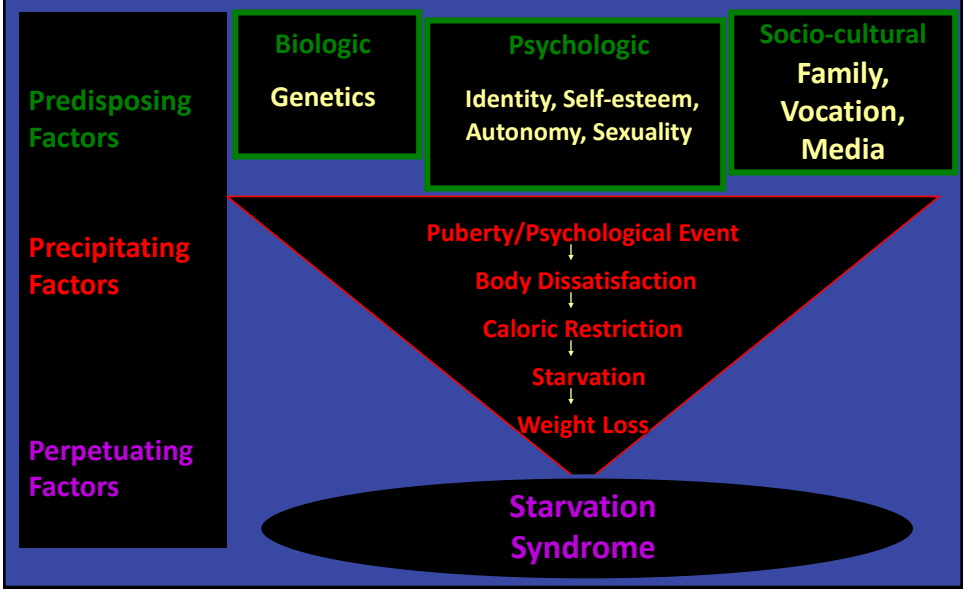
Why is that ?

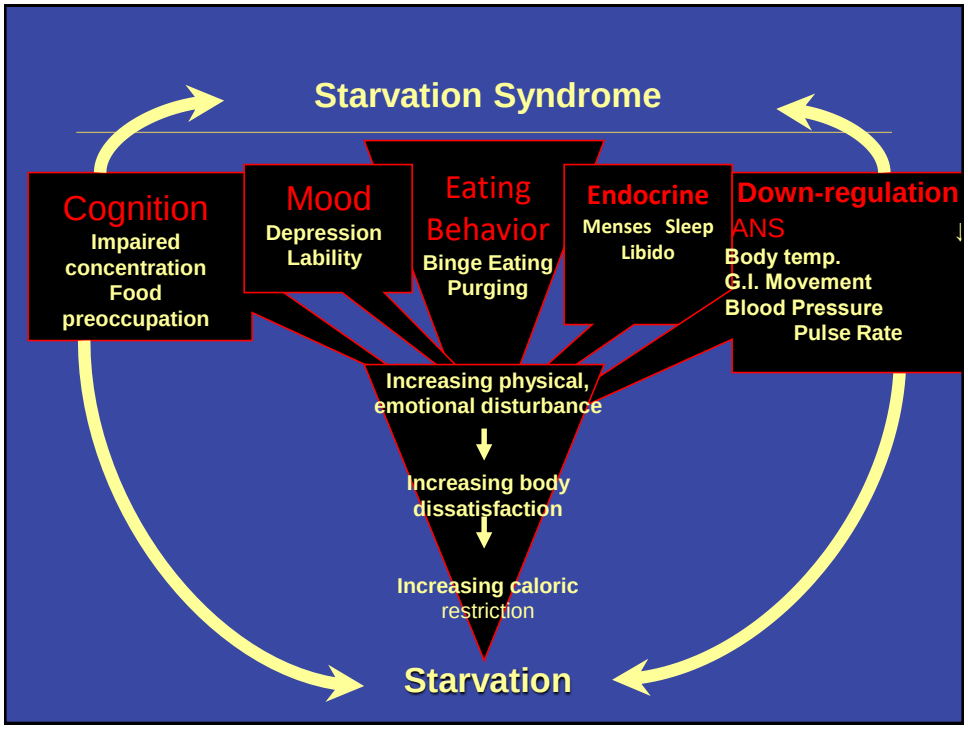
Why are Eating Disorders (EDs) Much More Common in Women than in Men?

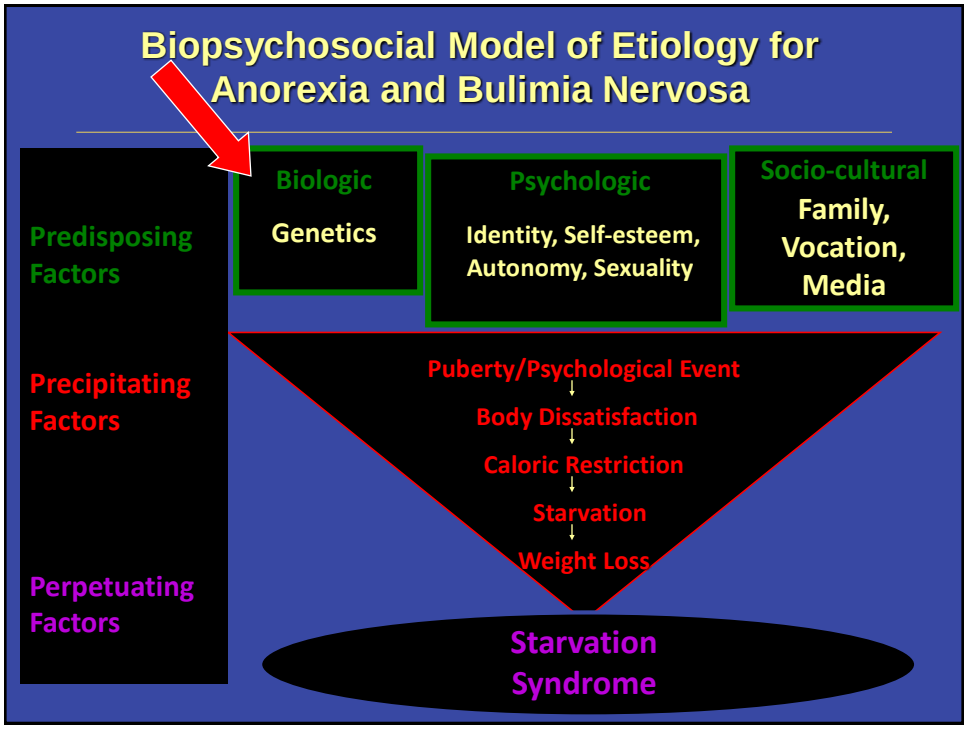
To answer this question, we need to consider the etiologic contribution to EDs of :

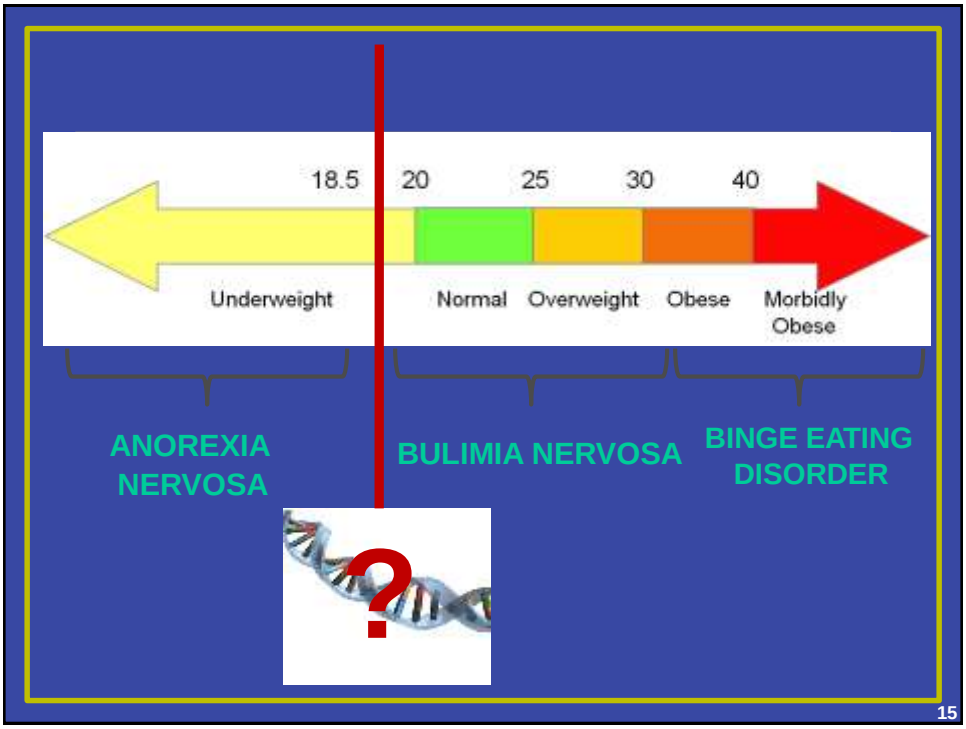
1. Genetics
2. Psychological factors
3. Environmental factors

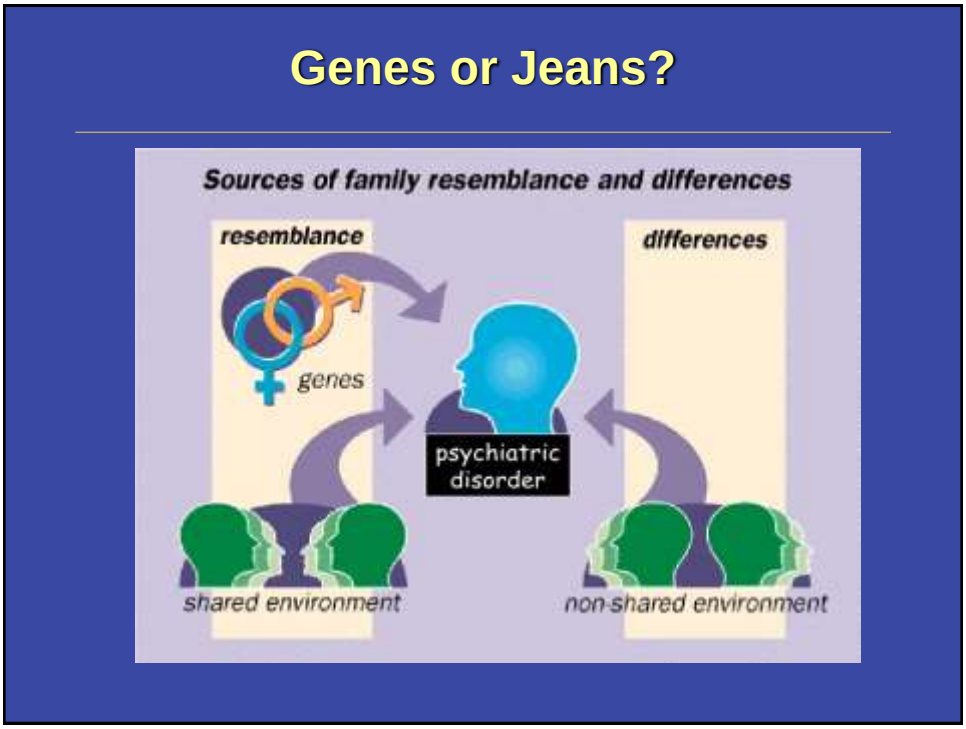
Biopsychosocial Model of Etiology for Anorexia and Bulimia Nervosa




Starvation Syndrome
Cognition
Impaired concentration
Food preoccupation
Mood
Depression
Lability
Eating Behavior
Binge Eating
Purging
Endocrine
Menses Sleep
Libido
Down-regulation
ANS
Body temp.
G.I. Movement
Blood Pressure
Pulse Rate
Increasing physical, emotional disturbance
Increasing body dissatisfaction
Increasing caloric restriction
Starvation


Biopsychosocial Model of Etiology for Anorexia and Bulimia Nervosa
Predisposing Factors
Precipitating Factors
Perpetuating Factors
Biologic
Genetics
Psychologic
Identity, Self-esteem, Autonomy, Sexuality
Socio-cultural
Family, Vocation, Media
Puberty/Psychological Event
Body Dissatisfaction
Caloric Restriction
Starvation
Weight Loss
Starvation Syndrome


18.5
20
25
30
40
Underweight
Normal
Overweight
Obese
Morbidly Obese
ANOREXIA NERVOSA
BULIMIA NERVOSA
BINGE EATING DISORDER
?
15


Genes or Jeans?
Sources of family resemblance and differences
resemblance
differences
genes
psychiatric disorder
shared environment
non-shared environment

Quantification of Effects

(A) Additive effects of genes

- complex trait
- influenced by many genes of small/moderate effect

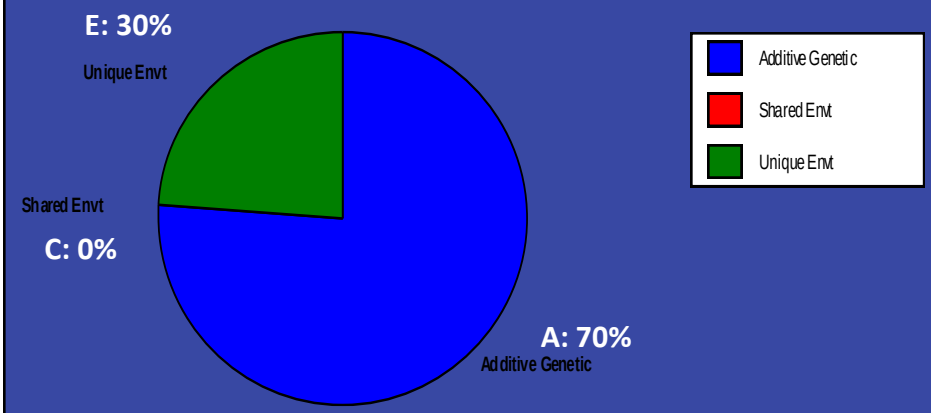
(C) "Shared" Environmental Effects

- religion
- parental rearing style
- socioeconomic status

(E) "Unique" Environmental Effects

- events experienced by one twin only

Heritability of Anorexia Nervosa



C. Bulik

What Do Twin Study Results Mean?

- Approximately 60-70% of variance in liability to eating disorders is due to additive genetic factors
- Impact of shared environment not substantial
- Both anorexia and bulimia nervosa appear to be markedly heritable

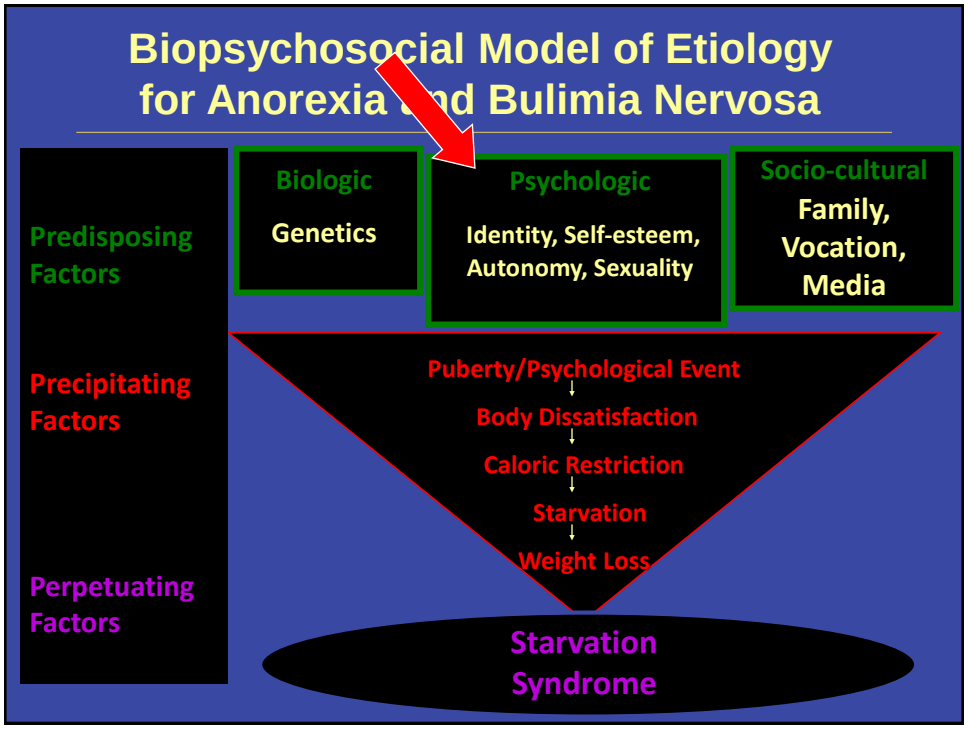
Whole Genome Wide Association Studies (GWAS) in AN

Psychiatric Genetics Consortium Eating Disorders Working Group – an international collaboration of researchers at multiple institutions worldwide.

The most powerful genetic study of anorexia nervosa conducted to date, included genome-wide analysis of DNA from 3,495 individuals with anorexia nervosa and 10,982 unaffected individuals. (AJP Duncan et al. Vol 174; No 9; Sept 2017, pp. 850-858)

Findings :

1. Identified one genome-wide significant locus for anorexia nervosa on chromosome 12, in a region previously shown to be associated with type 1 diabetes and autoimmune disorders.
2. Strong genetic correlations with various metabolic features including cholesterol, lipid and insulin-glucose metabolism- this has relevance to what we are discussing today.
3. Impact on treatment: viewing anorexia nervosa as both a psychiatric and metabolic condition could ignite interest in developing or repurposing medications for its treatment where currently none exist.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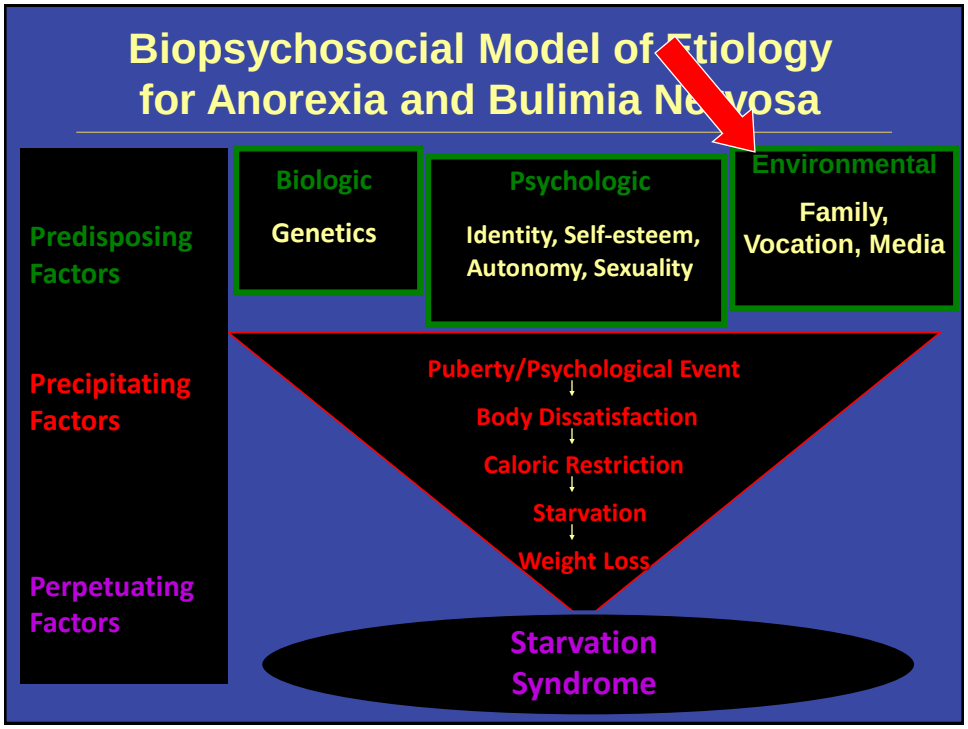
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Environmental Factors

1. Family

Can be protective by providing a forgiving environment or the family can magnify the cultural pressure for thinness and stigma against overweight/obesity

Know your child's vulnerabilities

Be mindful of activities that focus unduly on weight and shape and can potentially further damage child's self esteem (i.e., Gymnastics, Ballet, Modeling)

If you have a strong family history of alcoholism, would you encourage your child to become a bartender?

Environmental factors cont . . .

2. Media

- Glorifies and romanticizes eating disorders among the rich and famous
- Stigmatizes overweight/obese
- Engages in manipulation and falsification of images "photoshopping"

The famous faces of eating disorders

Nicole Richie

Paula Abdul

Alanis Morissette

Victoria Beckham

Elton John

Oprah Winfrey

Sandra Dee

Princess Diana

Jane Fonda

Michael Jackson

Mary-Kate Olsen

Lady Gaga

Richard Simmons

Joan Rivers

Portia de Rossi

Teasing Out Genetic and Environmental Effects

Gene X Environment Interaction

Genotype

aabb

AABB

Environment

Phenotype

"GENES LOAD THE GUN, THE ENVIRONMENT PULLS THE TRIGGER"

What Environmental Factors Increase the Vulnerability of Women to Eating Disorders (ED) ?

- Is it because women are more influenced by a weight obsessed culture (i.e, they read fashion magazines) ?
- Is it because women's self esteem is much more linked to body image than men ?
- Is it because because women are objectified in a misogynistic culture ?
- Is it because women are more likely to be sexually abused and traumatized than men ?

Why are Eating Disorders (ED) Much More Common in Women than Men?

- All of these factors increase the vulnerability of women to psychiatric disturbance in general (i.e., mood and anxiety disorders) but not specifically to ED.
- The specific vulnerability to ED relates to the fact that women's brains are much more sensitive to dietary intake that are men's brain

Gender Differences in Amino Acid Metabolism

- Tyrosine and tryptophan are essential amino acids and are the dietary sources of these brain amino acids.
- They are precursors for several brain neurotransmitters (serotonin and dopamine) and thus are of extreme importance for brain health.
- Both tyrosine and tryptophan share the same brain uptake system and compete for uptake into the brain with large neutral amino acids (LNAA-phenylalanine, isoleucine, valine)
- Carbohydrates stimulate insulin secretion, which drives LNAA into cells, leading to lower plasma levels of all the LNAA except for tryptophan
- Thus, tryptophan uptake to the brain is facilitated by CHO intake, resulting in higher brain levels and increased synthesis of serotonin

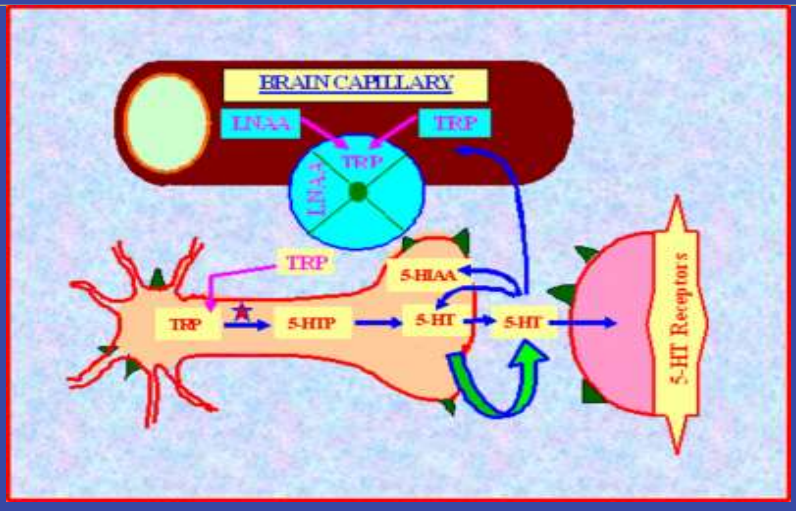
Gender Differences in Amino Acid Metabolism

- The mean rate of serotonin synthesis in normal males is 52% higher than in normal females; this marked difference may be a factor relevant to the higher incidence of major unipolar depression and eating disorders in females.
- Female brains are much more susceptible to Acute Tryptophan Depletion (ATD) than are male brains.
- Cowan et al (Adv Exp Med Biol 467;101-104; 1999) found that moderate dieting in healthy women but not in men lowered plasma tryptophan and impaired brain serotonin synthesis.
- ATD lead to relapse of bulimic and depressive symptoms in recovered BN and MDD subjects respectively. (Smith et al , Arch Gen Psych 56, 171-176, 1999)

Women more susceptible to the effects of dietary intake on central serotonin synthesis

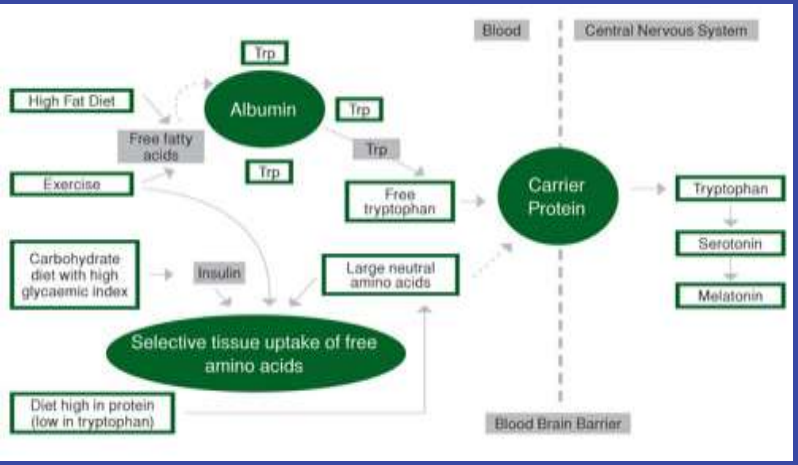
- Women are more likely than men to be dieting and as a result be on low calorie diets
- Low calorie diets tend to be high in protein and low in CHO and fat
- Such diets lead to tryptophan depletion and decreased serotonin synthesis in the brain
- Because of lower levels of central serotonin, women are more vulnerable to mood and eating disorders than men

5-HT is under the control of its circulating precursor TRP and the TRP/LNAA ratio, which determines brain levels of TRP and subsequently driving serotonin synthesis in the brain



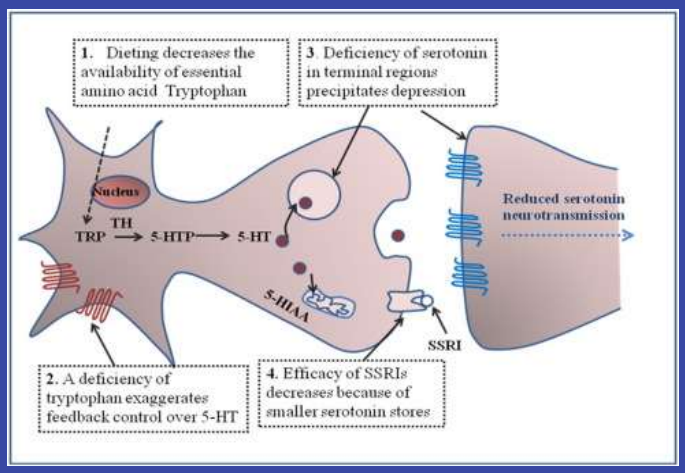
Adapted from Batool & Haleem, Internet Journal Pharmacology Vol 6, No 1

Effects of diet on tryptophan (Trp) uptake and synthesis of serotonin in the CNS



Adapted from Grimmett & Sillence, Veterinary Journal, 170 pp 24-32. (2005).

Why are SSRI's ineffective in the treatment of AN and its comorbidities ?



Haleem D. Life Sciences, Vol 178, June 2017, Pages 87-93

Tryptophan and Serotonin: The Bottom Line

- Tryptophan is an essential amino acid found mainly in high-protein animal foods.
- It's essential for the formation of serotonin — the neurotransmitter responsible for mood, sleep, learning/memory, and appetite control.
- Getting adequate tryptophan to create optimal levels of serotonin from food alone can be challenging.
- There are many reasons for this including, the paradox that protein blocks the formation of serotonin.
- Especially for women, eating a diet high in carbohydrates facilitates the formation of serotonin by stimulating insulin secretion which lowers the plasma level of all the LNAAs except for tryptophan, facilitating tryptophan transport into the brain and synthesis of serotonin

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More so for women than for men :

You are what you eat !

Thank you for your attention!

Differences Between Men and Women Regarding Nutrient Intake

DNA 98.5 % same

Nutrient intake:

- **Calories: Women- 5 ft 5in 120 lb 1800- 2000 cal/day**
  Men- 6ft 180 lbs 2800 cal/day
- **Protein: Women 42 grams /day; Men 58 grams/day**
- **Carbohydrates: lower for women, especially if on caloricallyrestricted diet**
- **Fat : Men, higher omega-3 alpha-linolenic acid (ALA) levels, increased risk of prostate CA.**
- **Calcium: Women- prevents osteoporosis**
  Men - elevated intake associated with increased incidence of prostate CA
- **Iron: Women need more than men; 18mg/day vs 8mg/day**