The “Detox Gene” and Estrogen

Dr. Andrew Rostenberg, DC, DIBAK

BEYOND GENETICS

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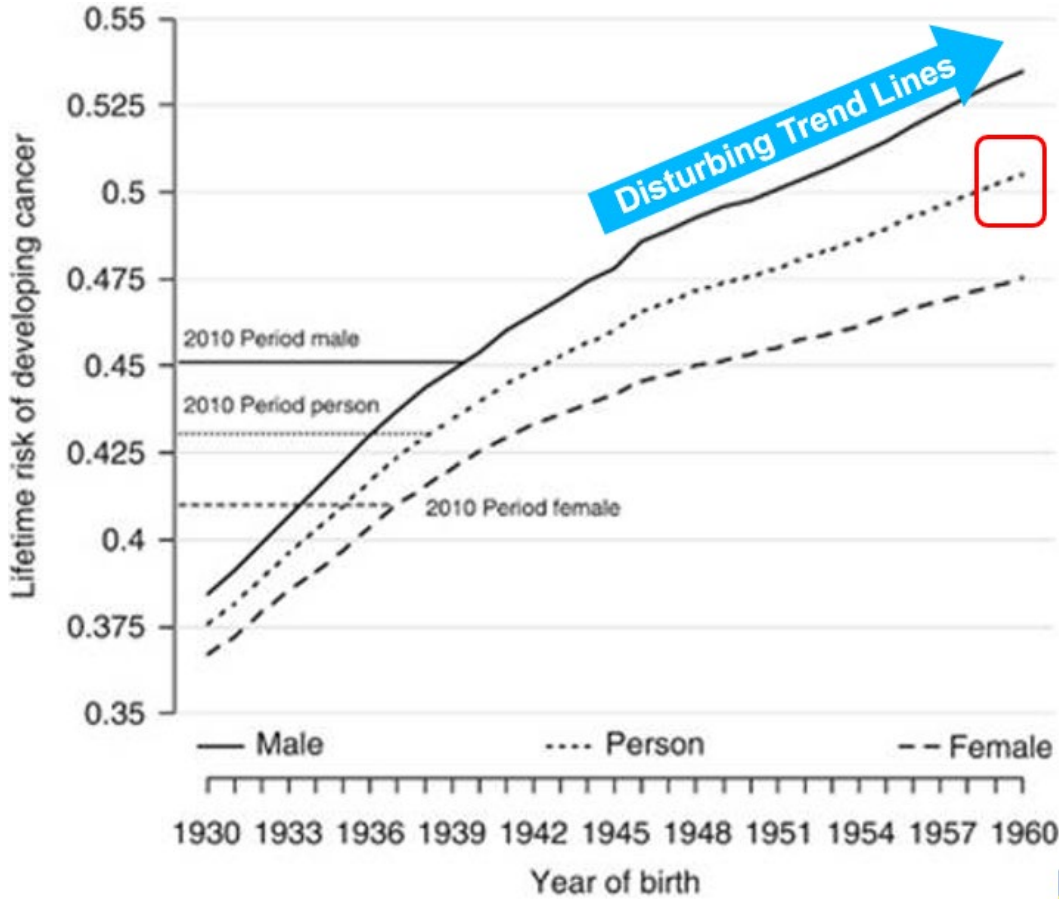
Cancer INCREASING, Now > 50% Chance



- The lifetime risk of cancer for people born since 1960 is >50%.
- **Over half of people** who are currently adults under the age of 65 years will be diagnosed with cancer at some point in their lifetime.

Br J Cancer. 2015 Mar 3;112(5):943-7. PMID: 25647015

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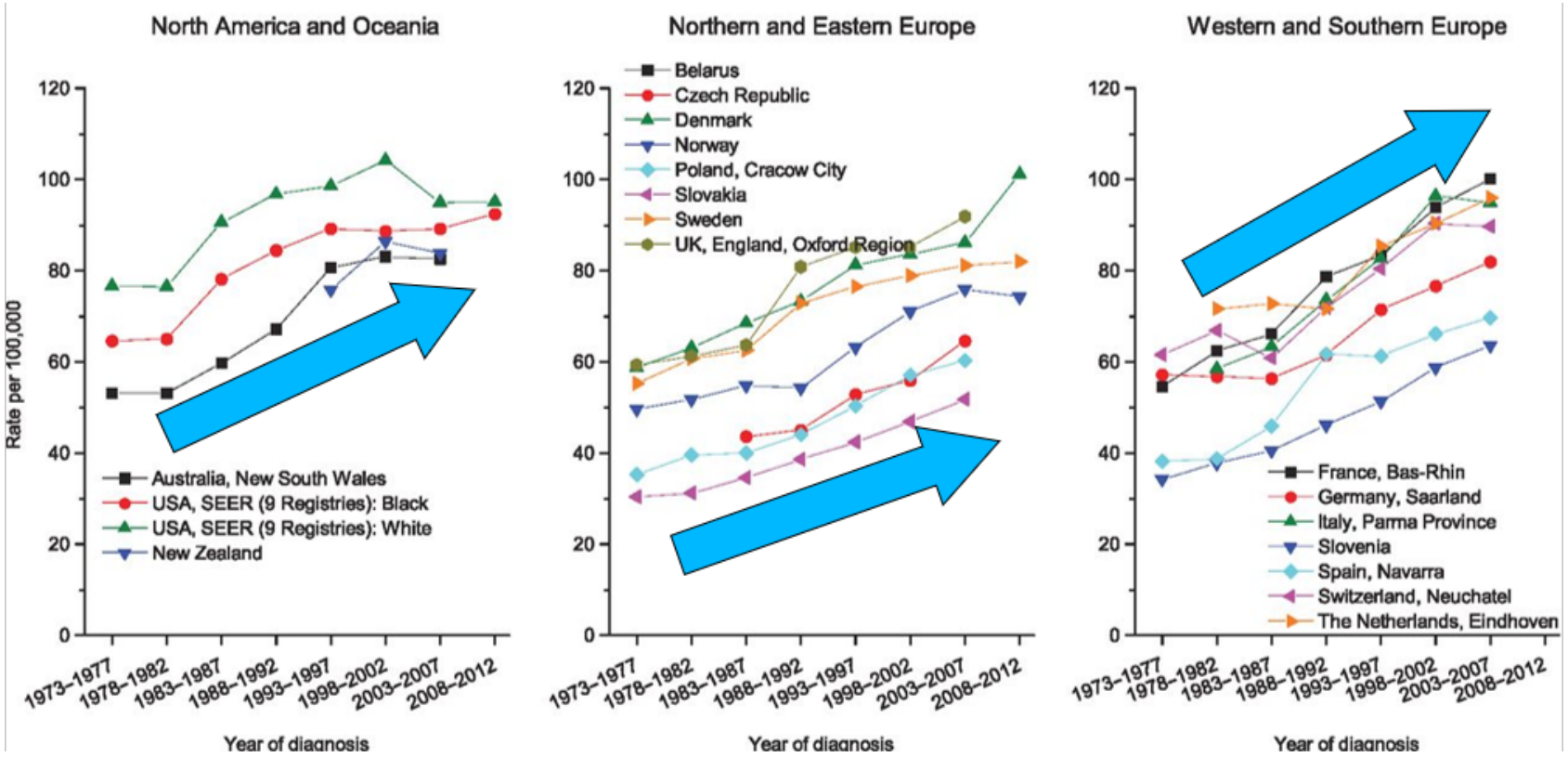
Breast Cancer Rates INCREASING



- Breast cancer is **the leading cause** of cancer-related death among females worldwide.
- In 2012, an estimated 1.7 million cases and 521,900 deaths occurred.

Cancer Epidemiol Biomarkers Prev. 2016 Jan;25(1):16-27.
PMID: 26667886

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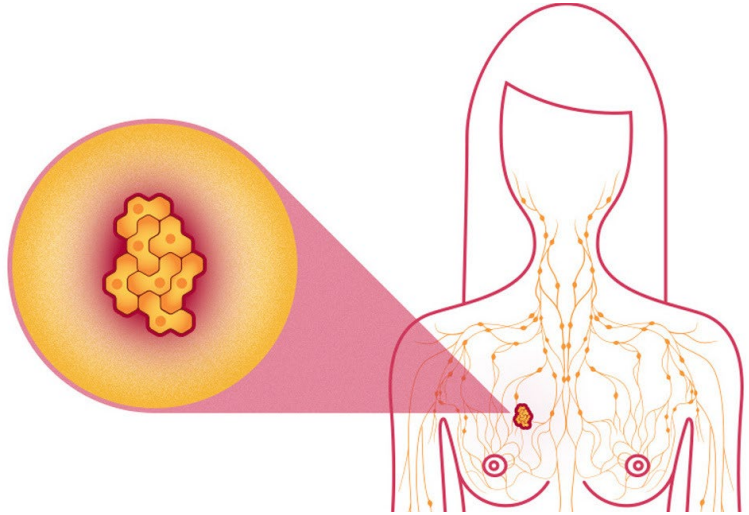
Modern BC STILL Causing CANCER



- Among 1.8 million women who were followed on average for 10.9 years (a total of 19.6 million person-years), 11,517 cases of breast cancer occurred.
- As compared with women who had never used hormonal contraception, the relative **risk of breast cancer** among all current and recent users of hormonal contraception was 1.20 (95% confidence interval [CI], 1.14 to 1.26).
- This risk increased from 1.09 (95% CI, 0.96 to 1.23) with less than 1 year of use to 1.38 (95% CI, 1.26 to 1.51) with more than 10 years of use (P=0.002).

N Engl J Med. 2018 Mar 29;378(13):1265-1266. PMID: 29590551

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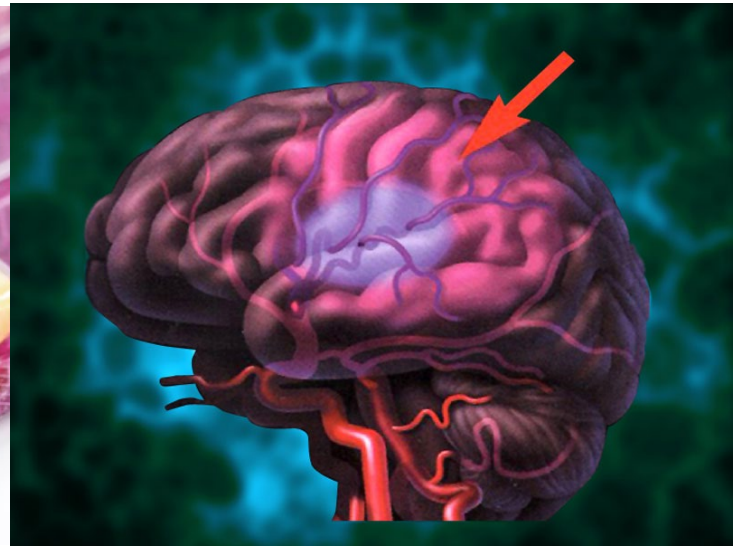
Birth Control INCREASES STROKE by 50%



- In oral contraceptive users, *plasma levels of practically all coagulation factors increase*.
- In particular, Factor VII and X may increase by up to 170% of their baseline values, whereas fibrinogen levels usually increase by 10–20% of baseline values…
- This therapy increases by twofold **the relative risk of venous thromboembolism** (VTE) and **by 50% that of fatal or disabling stroke** while also increasing the early risk of myocardial infarction and having no protective effect against coronary heart disease after longer-term use.

Toxicol Pathol. 2007 Feb;35(2):208-25. PMID: 17366315

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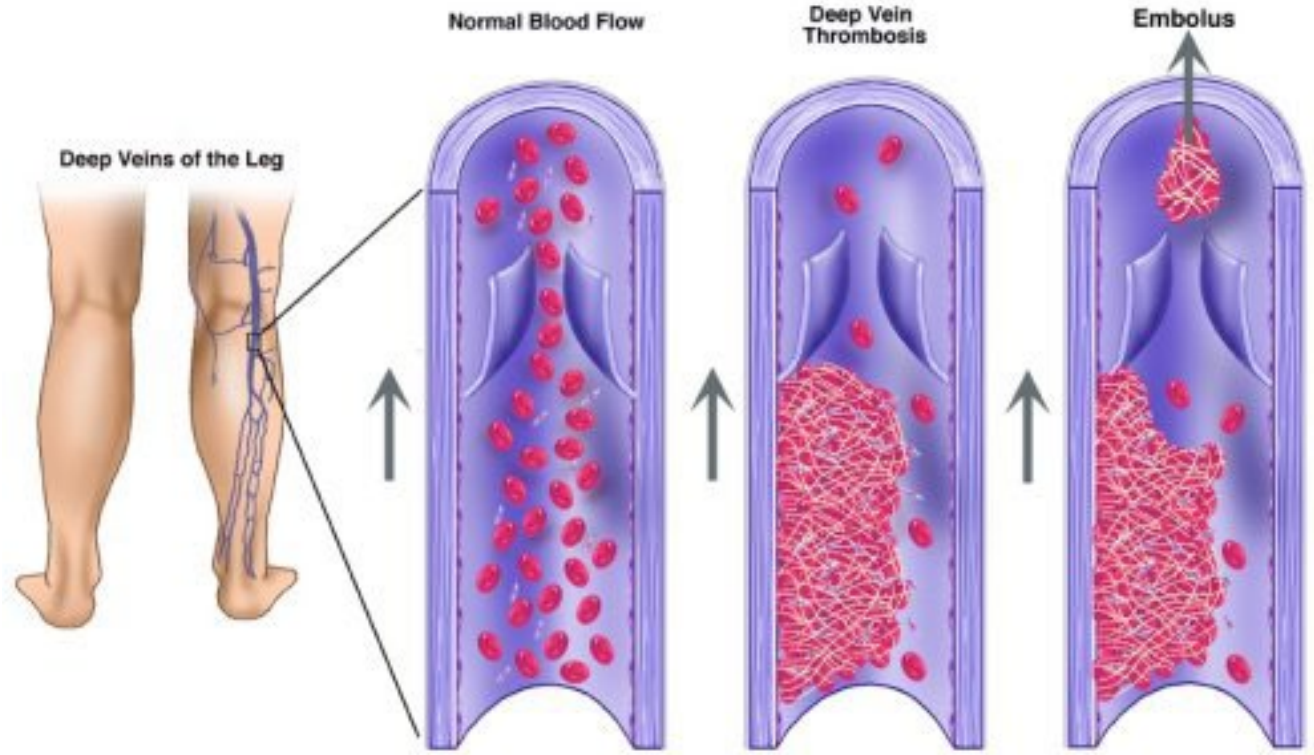
High Estrogen, Coagulated Blood, Blood Clots, Stroke



- Use of oral contraceptives (OC) that combine a progestogen with synthetic ethinyl estradiol (EE) is associated with **increased risk** of venous thromboembolism.

Thromb Haemost. 2011 Mar;105(3):560-7. Epub 2011 Jan 12.
PMID: 1225090

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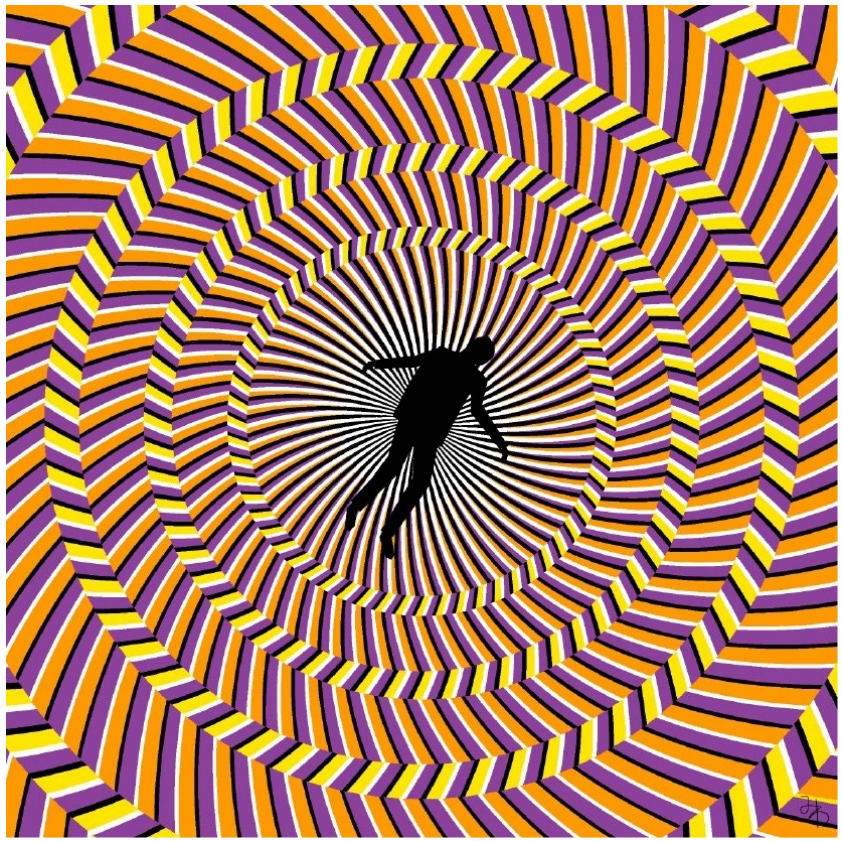
High Estrogen, Coagulated Blood, Less Blood to Brain



- The aim of the study was to evaluate the correlation between **hormonal contraceptives and sex hormones levels as a possible cause of vertigo** related to coagulation disorders and fibrinolyse…
- An increased concentration of estrogens in serum may have an additional negative effect on a possibility of a thromboembolic episode.
- In the female patients interested in oral contraception, the prophylactic exclusion of risk factors for a thromboembolic disease seems to be vital.

Otolaryngol Pol. 2013 Jan;67(1):25-9. PMID: 23374660

Exposure Begins BEFORE BIRTH

THURSDAY, JULY 14, 2005

BODY BURDEN: THE POLLUTION IN NEWBORNS

Body Burden: The Pollution in Newborns

- In a study spearheaded by the Environmental Working Group (EWG) in collaboration with Commonweal, researchers at two major laboratories found an average of **200 industrial chemicals and pollutants** in umbilical cord blood from 10 babies born in August and September of 2004 in U.S. hospitals…
- Of the 287 chemicals we detected in umbilical cord blood, we know that 180 cause cancer in humans or animals, 217 are toxic to the brain and nervous system, and 208 cause birth defects or abnormal development in animal tests.
- The dangers of pre- or post-natal exposure to this complex mixture of carcinogens, developmental toxins and neurotoxins have never been studied.

https://www.ewg.org/research/body-burden-pollution-newborns

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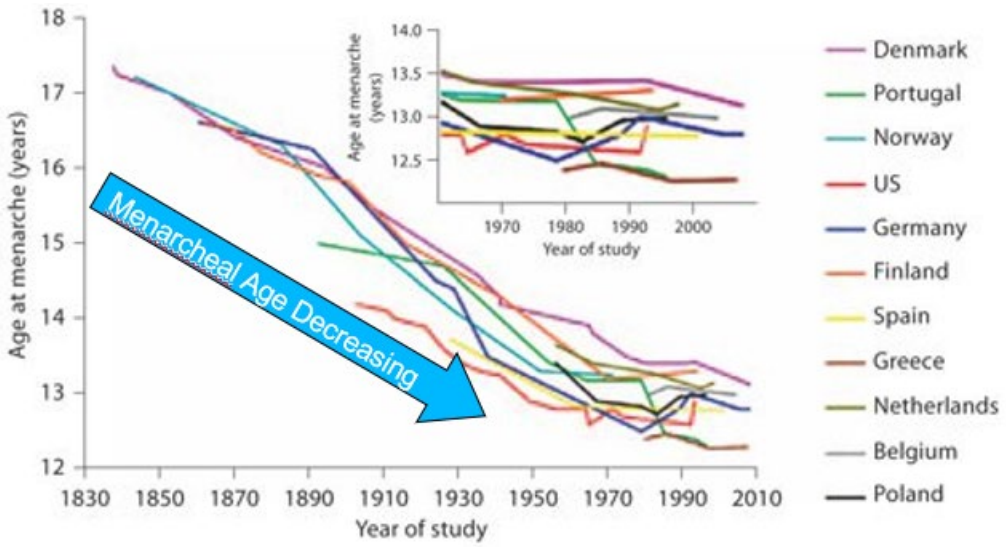
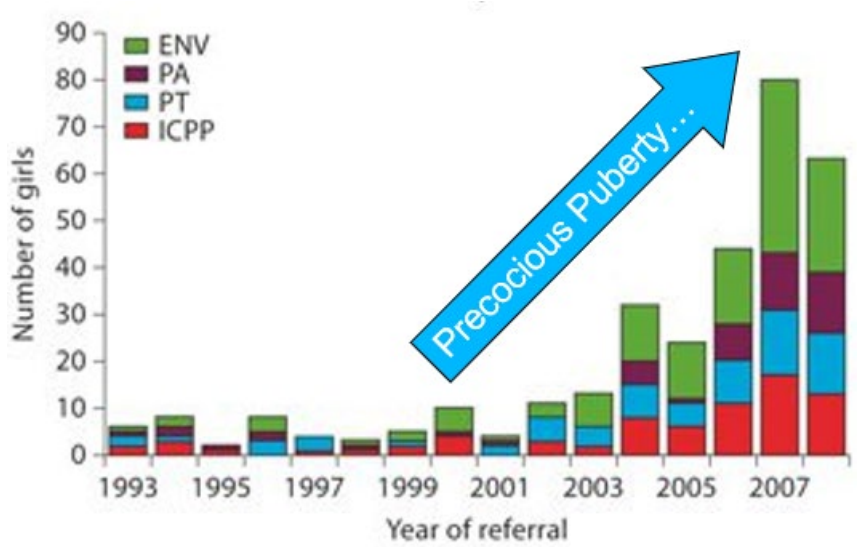
Precocious Puberty INCREASING

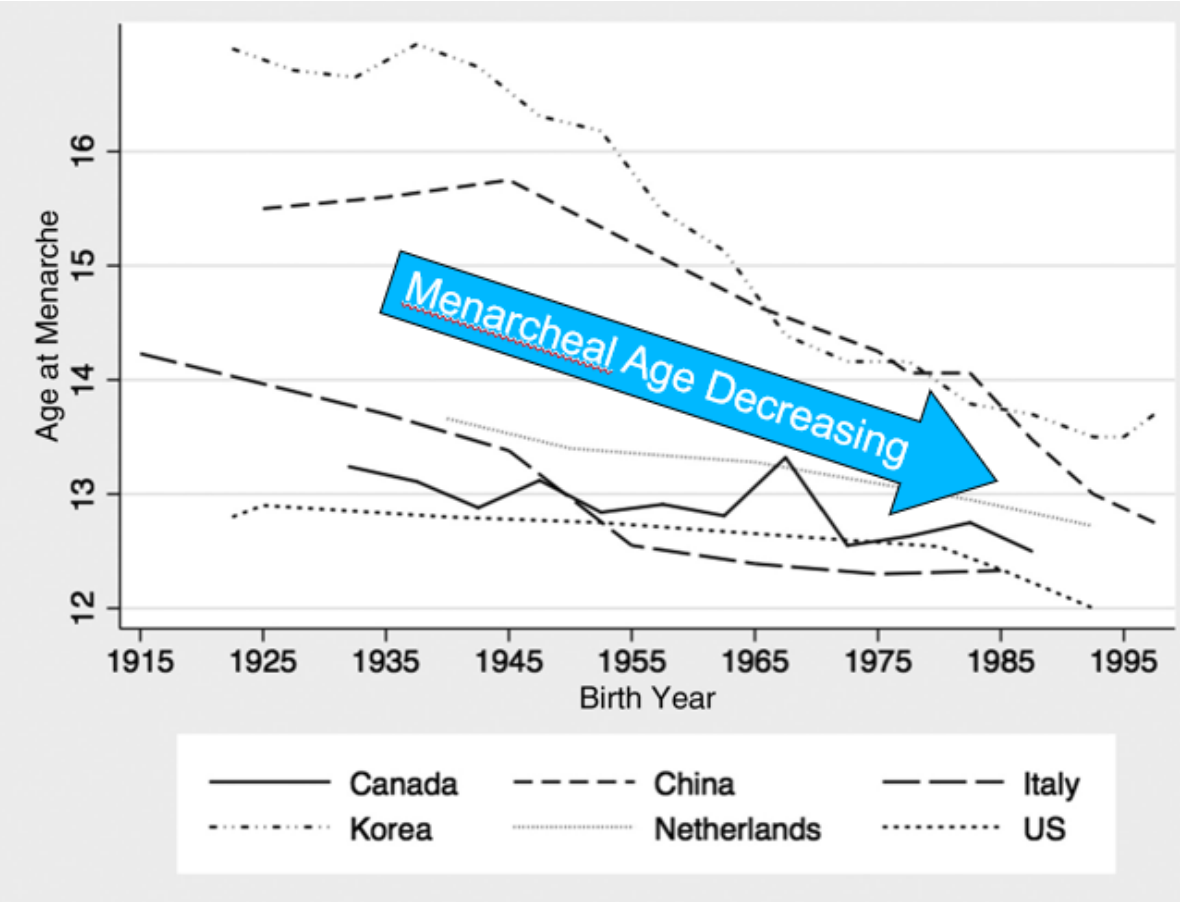




- Before the 1980s, the mean **age at onset** of breast development was consistently reported to be approximately 11 years in both American and European studies.
- However, data from the American population-based Third National Health and Nutrition Examination Survey (NHANES III) conducted from 1988 to 1994 showed mean ages at onset of puberty in girls **well below 10 years**.

Horm Res Paediatr. 2012;77(3):137-45. PMID: 22508036

Age of Menarche DECREASING



- The age at menarche declined from 14.25 in Chinese girls born before 1976 to 12.60 in girls born after 2000, with an estimated decline of **0.51 years per decade** (P < .001).
- The downward trend of age at menarche for rural girls was greater than for urban girls (0.62 vs 0.35 years per decade; P < .001).

Pediatrics. 2017 Aug;140(2). pii: e20170085. PMID: 28716824

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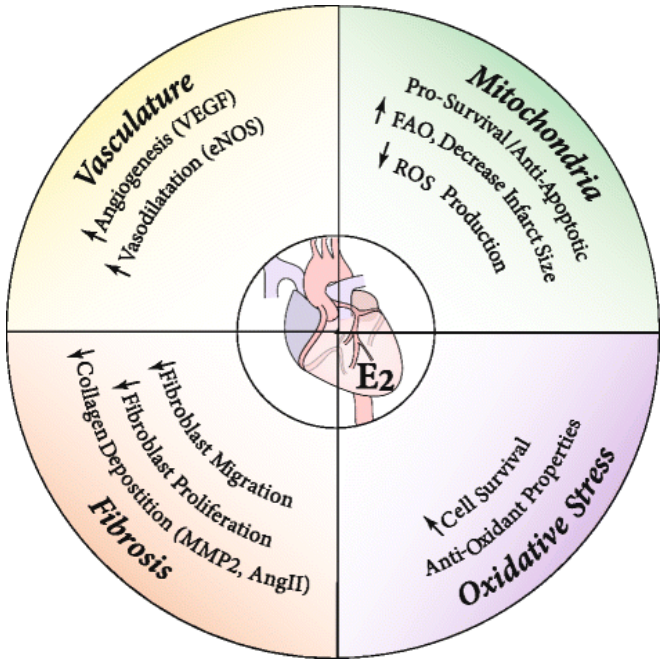
Estrogen OVERVIEW

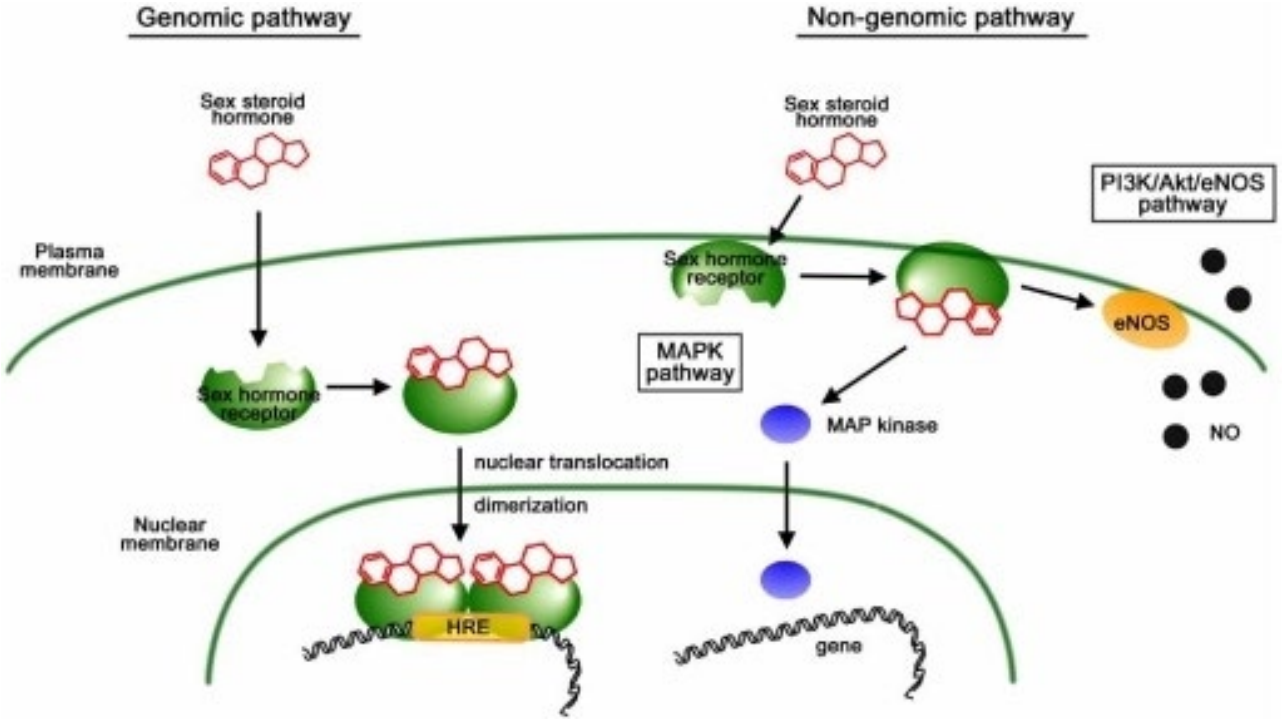


- *Epidemiologic studies have previously suggested that premenopausal females have reduced incidence of cardiovascular disease (CVD) when compared to age-matched males, and the incidence and severity of CVD* ***increases postmenopause****.*
- Biol Sex Differ. 2017 Oct 24;8(1):33. PMID: 29065927

Generally, women suffer less life-threatening and chronic illnesses than men, such as cardio(cerebro)vascular diseases, certain cancers, chronic fibrogenic disorders (atherosclerosis, renal and liver fibrosis), and emphysema. Compared with age-adjusted men, women have lower mortality rates **for the 15 leading causes of death…**

Oncotarget. 2017 May 31;8(57):97683-97692. PMID: 29228643

Non-Genomic Effects of Estrogen



- In addition to the effects on the female reproductive functions, estrogens also **play a significant role** in the regulation of skeletal homeostasis, lipid and carbohydrate metabolism, electrolyte balance, skin physiology, the cardiovascular system and the central nervous system.

Biochem Med (Zagreb). 2014 Oct; 24(3): 329–342. PMCID: PMC4210253

Key Concept

Excessive Estrogen ≠ Excessive E1, E2 or E3

- Any estrogenic ligand (bioidentical HRT, EDCs, Metalloestrogens, Mold biotoxins, etc.) in excess **could trigger estrogen-response elements in any location, in any tissue and at any time all over the body.** Think BEYOND HORMONES and more about the total environmental, estrogenic load.

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Mycoestrogens Are TOXIC ESTROGENS

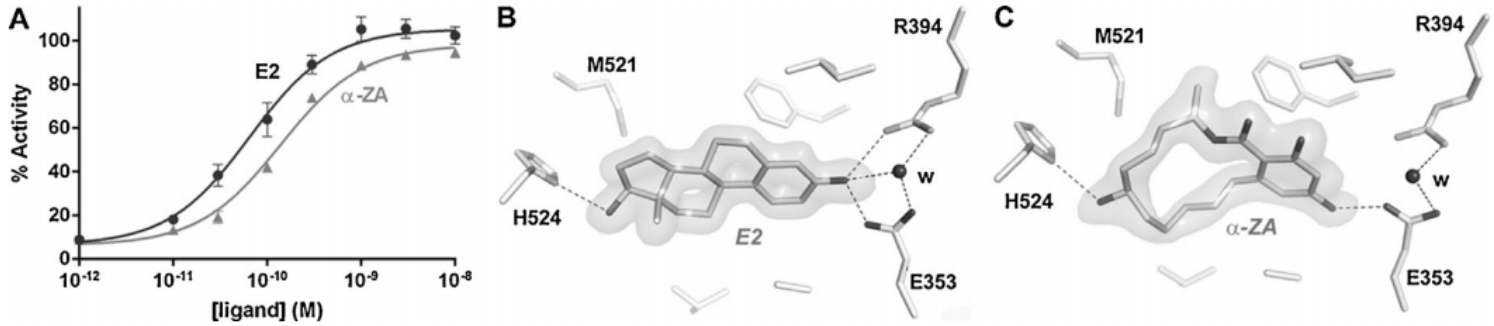

Fig. 2. The mycoestrogen α-zearalanol is a full estrogen (ERα) agonist. Relative transcriptional activity of ERα in HGELN-ERα cells in the presence of estradiol or α-zearalanol (100% as 10 nM E2) (**A**). Interaction networks of estradiol (**B**) and α-zearalanol (**C**) with residues of the ERα–ligand-binding domain (LBD). The volume around the ligands represents their electron density.

- The smallest compounds making fewer contacts with the receptor cavity are generally associated with lower binding affinities, whereas bigger EDCs adopting a binding mode reminiscent of that used by the endogenous ligands are characterized by higher interaction capacities.
- This is, for example, the case of the mycoestrogen α-zearalanol (α-ZA), which **acts as a full ERα agonist** (Fig. 2A) and binds to ERs with high-affinity (Kd of 0.29 nM and 1.88 nM for ERα and ERβ, respectively, to be compared to 0.017 nM and 0.068 nM for E2).

C R Biol. 2017 Sep - Oct;340(9-10):414-420. PMID: 29126514

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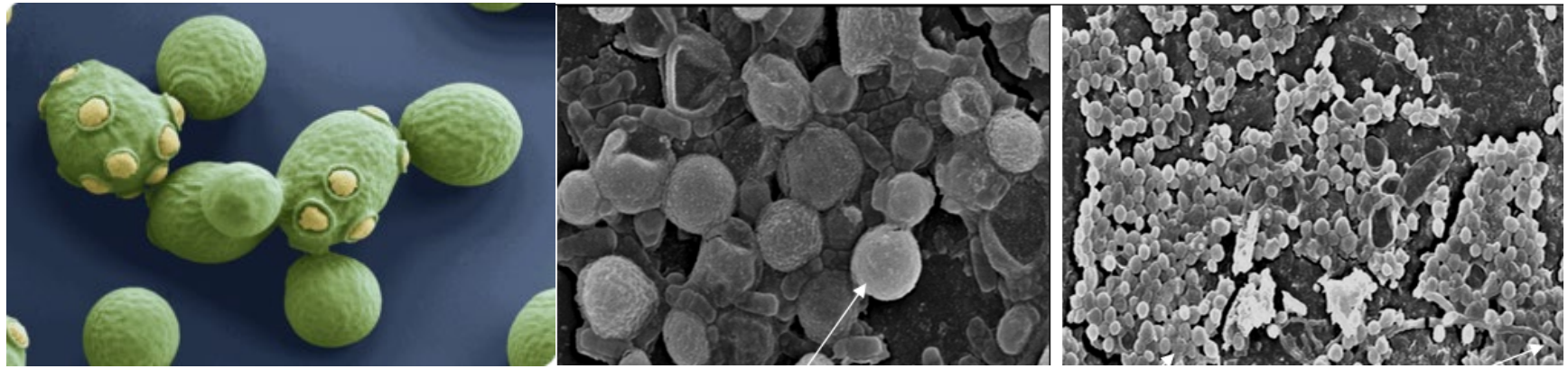
Estrogen STIMULATES 8X Candida Growth



- Estradiol (E(2)) stimulates colonization of the vagina by Candida albicans.
- Although this yeast expresses an estrogen-binding protein (EBP), the cellular target for estrogenic modulation of this infection is unresolved.
- Findings support direct E(2)-induced C. albicans growth as well as indirect effects via E(2)-induced changes in the vaginal epithelium… We confirmed that our isolate of C. albicans contained a high-affinity EBP, with no detectable affinity for DES.
- **Vaginal colonization by C. albicans was 8.6-fold greater** in response to in vivo treatment with E(2) than with the comparable dose regimen of DES.

J Surg Res. 2005 Dec;129(2):278-82. PMID: 16111702

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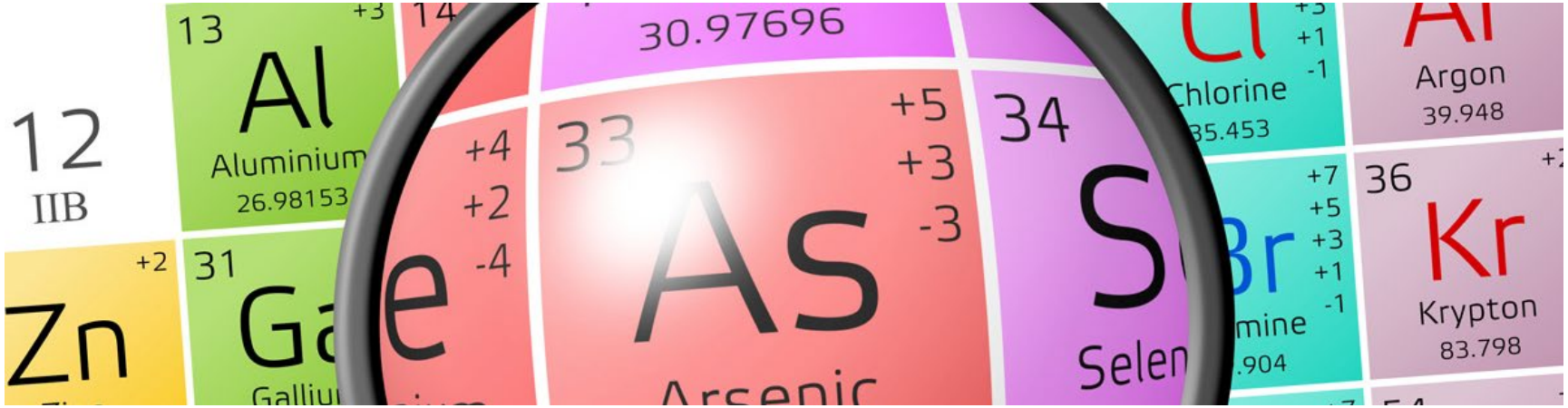
Metalloestrogens BIND Nuclear Estrogen Receptors



- Recent reports of the ability of certain metal ions to also bind to oestrogen receptors and to give rise to oestrogen agonist responses in vitro and in vivo has resulted in the realisation that environmental oestrogens can also be inorganic and such xenoestrogens have been termed metalloestrogens.
- This report highlights studies which show metalloestrogens to include **aluminium, antimony, arsenite, barium, cadmium, chromium (Cr(II)), cobalt, copper, lead, mercury, nickel, selenite, tin and vanadate.**
- The potential for these metal ions to add to the burden of aberrant oestrogen signalling within the human breast is discussed.

J Appl Toxicol. 2006 May-Jun;26(3):191-7. PMID: 16489580

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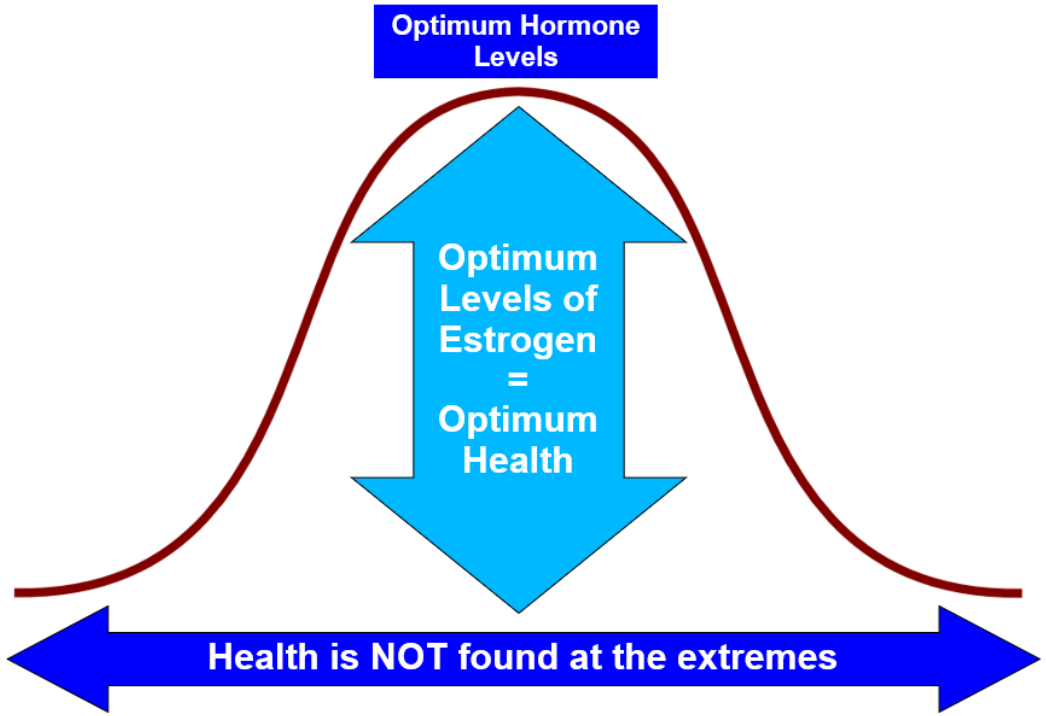
Estrogen Bell Curve

Hormone Deficiency

Low Estrogen
Stroke
Dementia
Depression
Cardiovascular Disease
Hot Flashes
Choline Deficiency
Amenorrhea
Osteoporosis
Prolapsed Uterus
Fast COMT/MAO



Hormone Excess

High Estrogen
Stroke, Embolisms, Clots
Anti-Thyroid
PMS, Anemia
Anxiety/Worry/Panic
Promotes Cancer
Fibroids, Tumors
Endometriosis
GB Disease
Slow COMT/MAO

** Estrogen excess can be relative, ie caused by low progesterone OR by normal progesterone levels and ELEVATED estrogen, both natural and synthetic.

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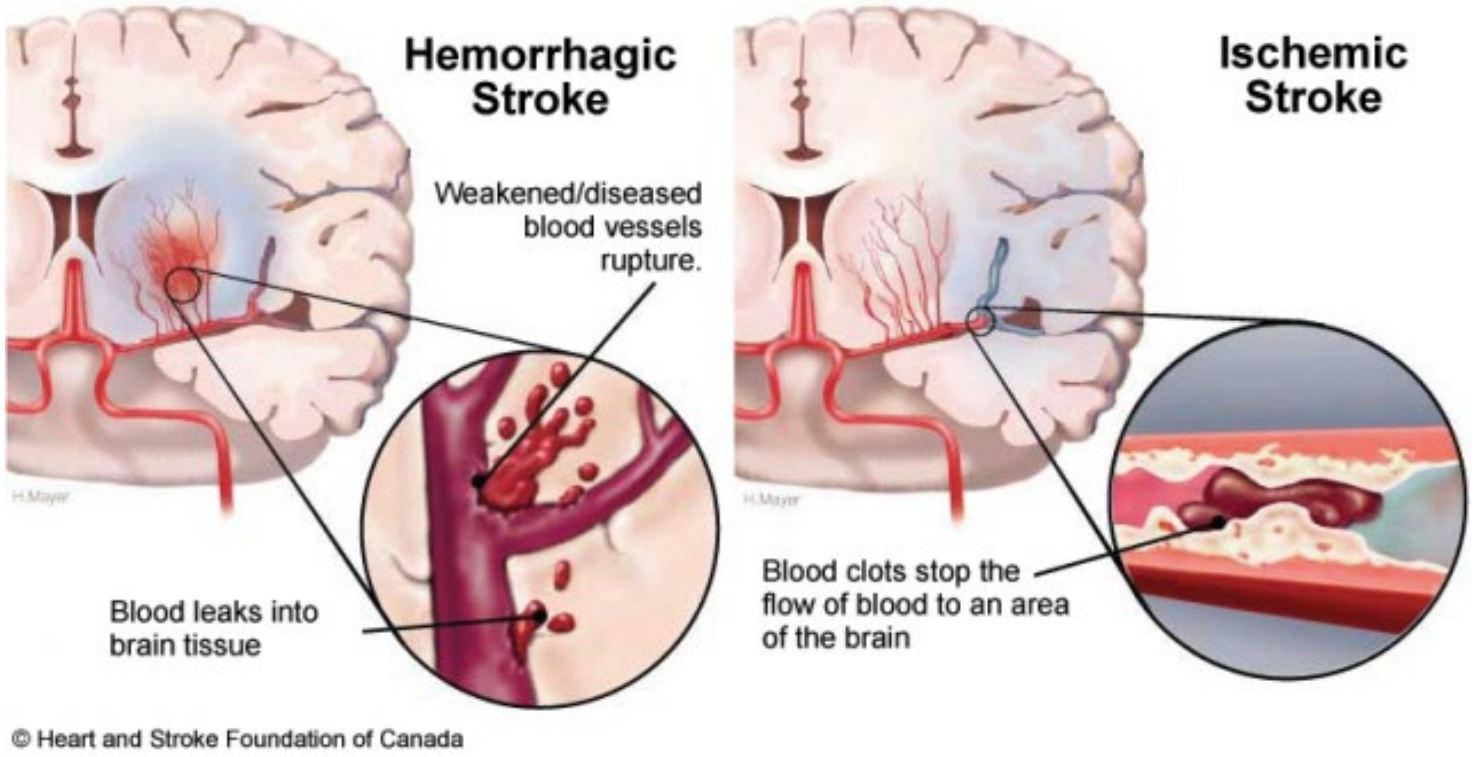
Post-Menopausal Women Higher CVD Risk



- In women, the risk of CVD is much lower than in men until 50 years of age, **but it rises dramatically after menopause.**
- It has been hypothesized that **lower levels of endogenous estrogens** and higher endogenous androgens that occur as a consequence of the menopausal transition **might mediate the increased CVD risk later in life in post-menopausal women.**

J Am Coll Cardiol. 2018 Jun 5;71(22):2555-2566. PMID: 29852978

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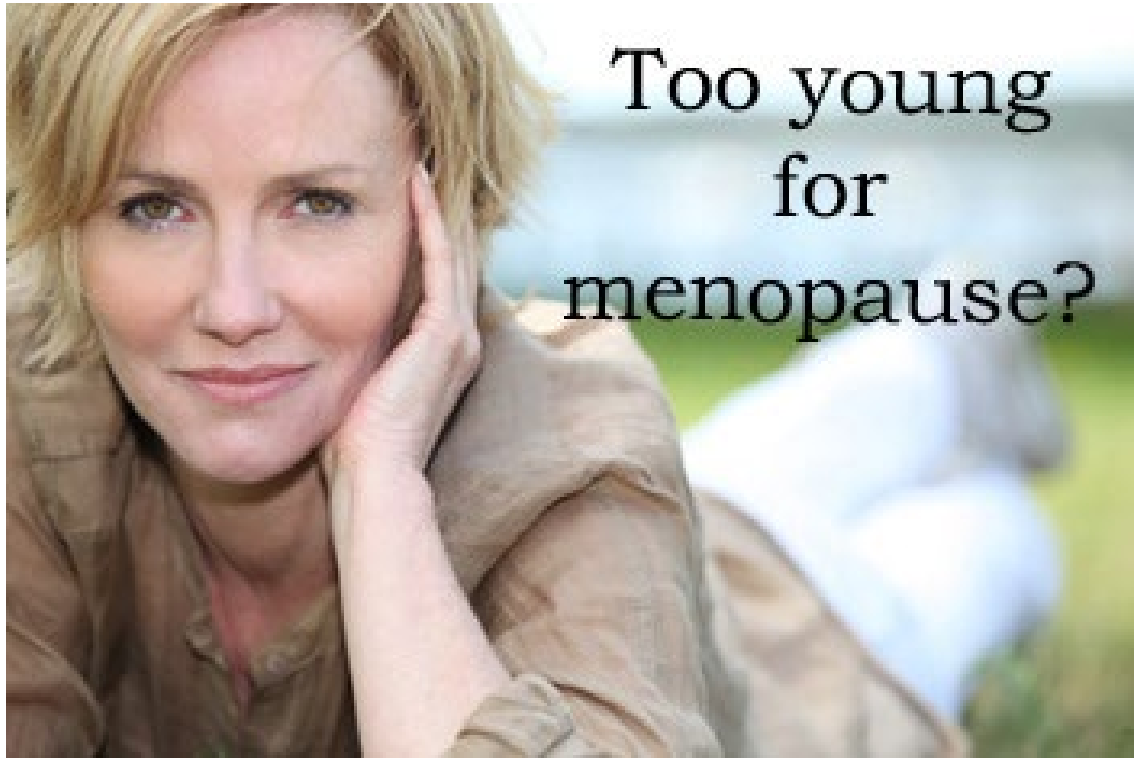
Women Have More Strokes, Worse w/ Early Menopause



Premature or early-onset menopause in women younger than 45 years were **associated with an increased risk of coronary heart disease and all-cause mortality**...the relative risks (95% CIs) were **1.50 (1.28-1.76) for overall CHD**, 1.11 (1.03-1.20) for fatal CHD, **1.23 (0.98-1.53) for overall stroke**, 0.99 (0.92-1.07) for stroke mortality, 1.19 (1.08-1.31) for CVD mortality, and 1.12 (1.03-1.21) for all-cause mortality.

JAMA Cardiol. 2016 Oct 1;1(7):767-776. PMID: 27627190.

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MTHFR = Bottle Neck for Estrogen Detoxification

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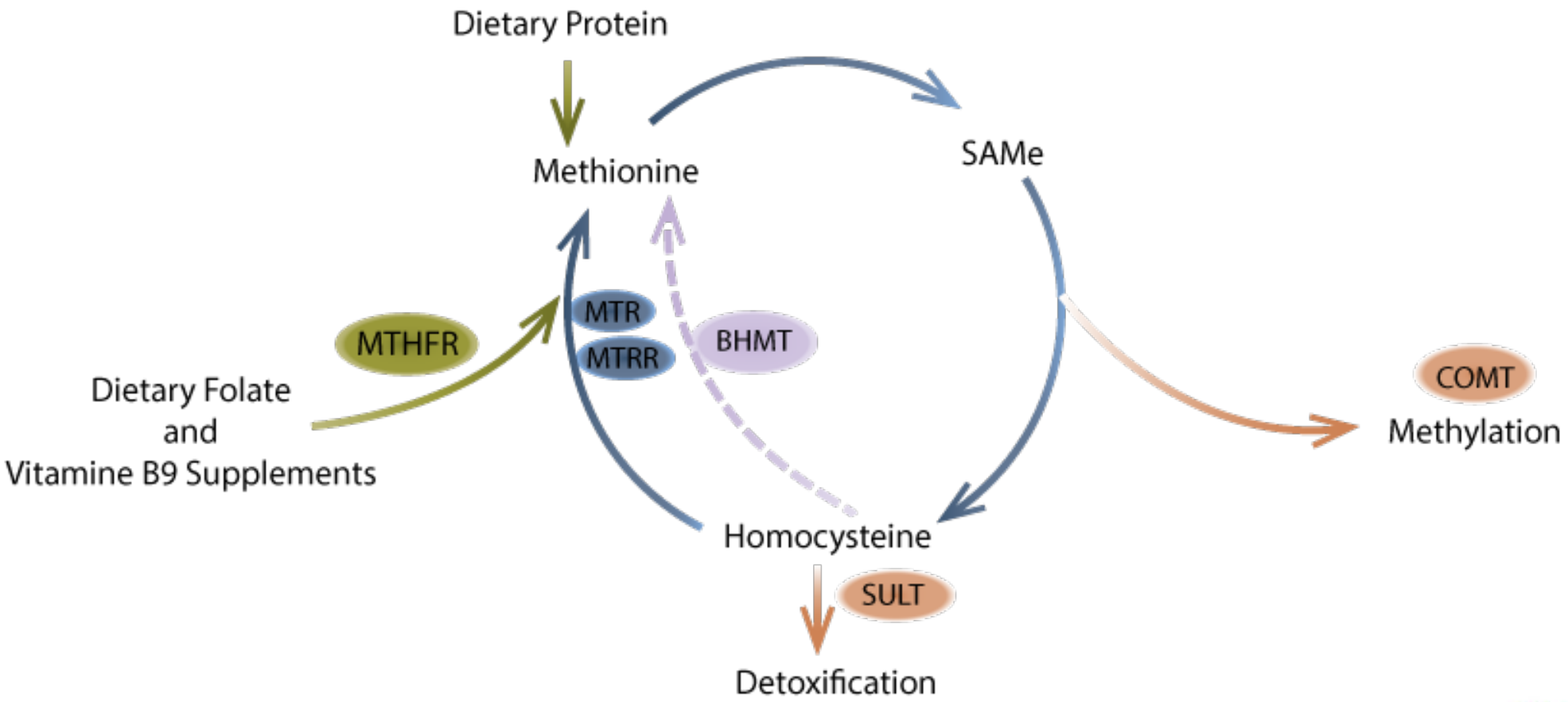
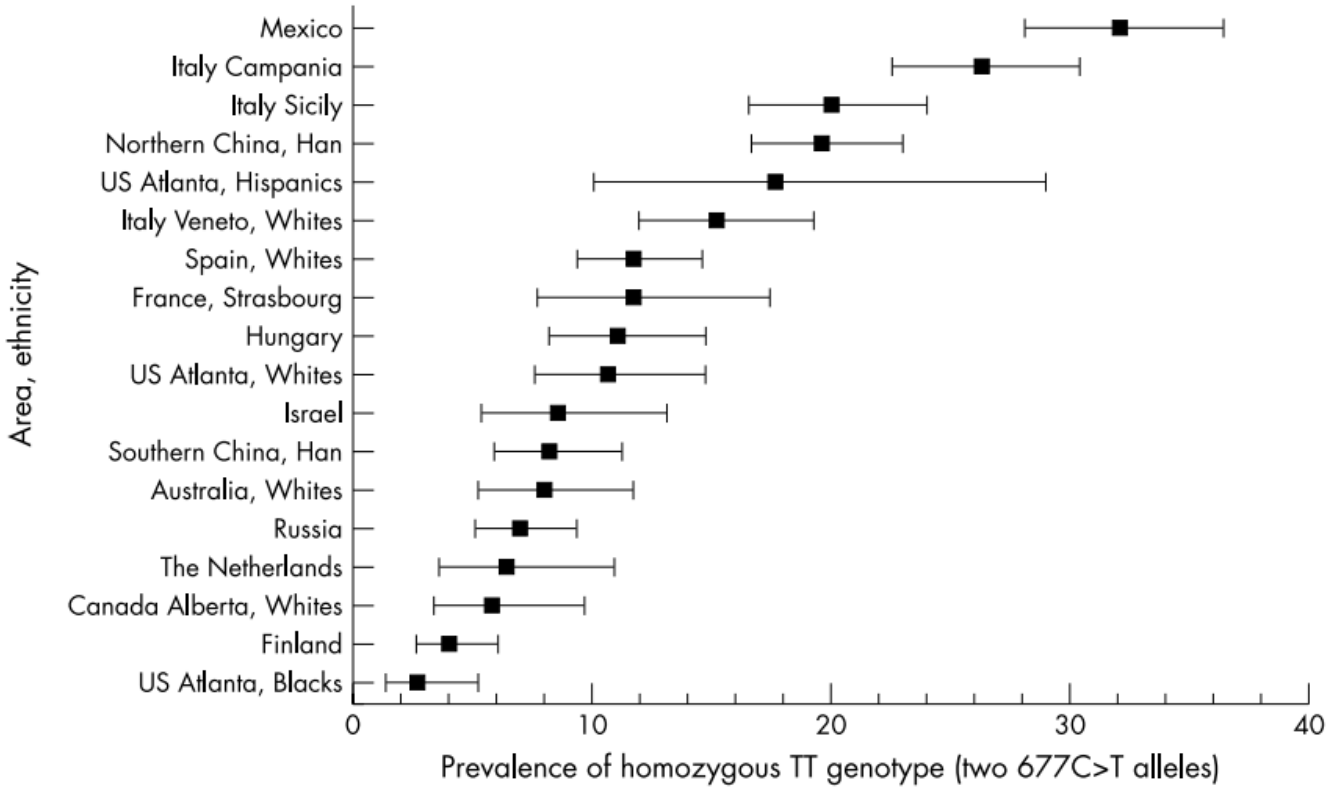
Methylation Cycle – Elegant Biochemistry



MTHFR WORLD-WIDE DISTRIBUTION



- The distribution of the allele showed marked ethnic and geographical variation The homozygous TT genotype was particularly common in northern China (20%), southern Italy (26%), and Mexico (32%).
- There was also some evidence for geographical gradients in Europe (north to south increase) and China (north to south decrease).
- The TT genotype frequency was low among newborns of African ancestry, intermediate among newborns of European origin, and high among newborns of American Hispanic ancestry.

J Med Genet. 2003 Aug; 40(8): 619–625. PMCID: PMC1735571

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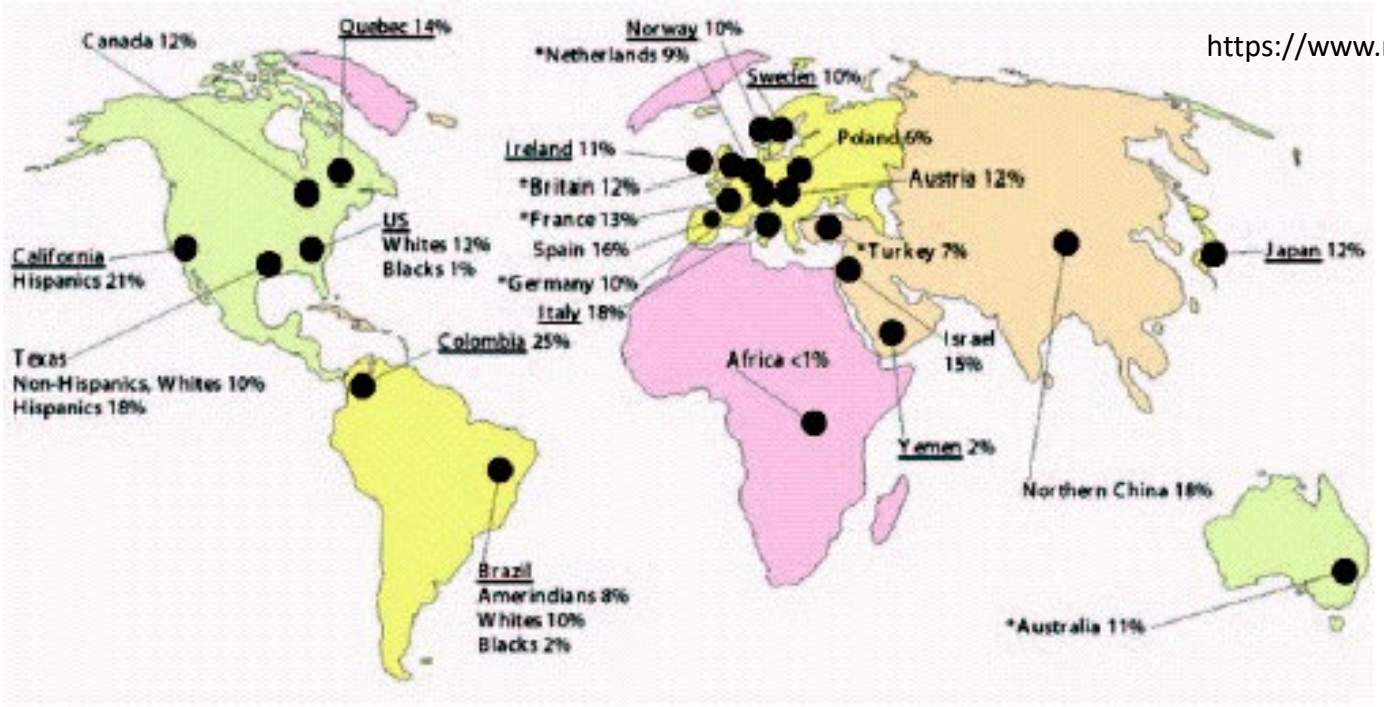
Global Distribution of MTHFR Genes



https://www.ncbi.nlm.nih.gov/books/NBK6561/

- **The heterozygous 677CT genotype ranges from 13% in Africans to 51% in Italians and 44% in North American Caucasians.** The homozygous 677TT rate in the last group is 12%. The prevalence of heterozygous genotype 1298AC among Caucasians in the United States was 47%, and that of the homozygous 1298AA mutant allele was 7.9%.

Journal of American Physicans and Surgeons 2004; 9:106–8.
https://www.jpands.org/vol9no4/boris.pdf

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Homozygous VS. Heterozygous

- The data demonstrate that 677C T polymorphisms, whether homozygous or heterozygous, are significantly associated with ASD.
- The homozygous (TT) individuals are reported to have **an approximately 50% decrease in MTHFR enzyme activity, and the heterozygous (CT) a 30% decrease in enzyme activity** as measured in their lymphocytes

Journal of American Physicans and Surgeons 2004; 9:106–8.
https://www.jpands.org/vol9no4/boris.pdf

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Compound Heterozygous 60% Reduction

- Enzyme activity and thermolability were assessed in bacterial extracts.
- The activity of the wild-type cDNA was designated as 100%; mutant enzymes containing the 1298 and 677 mutations separately had 68% (+/-5.0) and 45% (+/-10.8), respectively, of control activity while **the enzyme containing both mutations had 41% (+/-12.8) of control activity.**
- The 1298 mutation was not associated with a thermolabile enzyme.

Atherosclerosis. 2001 Jun;156(2):409-15. PMID: 11395038

MTHFR & MTRR 15X HIGHER in Women w/ Spontaneous Abortions

- The distribution frequency (18/118, 15.3%) of the MTHFR 677TT genotype was significantly higher in the abortion group ($\chi 2 = 11.006$, $P = 0.004$) than in the control group (2/174, 1.1%); on the other hand, the distribution frequency of the MTHFR A1298C genotype did not significantly differ between the abortion and control groups ($\chi(2) = 0.441$, $P = 0.507$).
- The distribution frequency of the MTRR A66G genotype was also significantly higher in the abortion group (14/118, 11.9%; $\chi(2) = 10.503$, $P = 0.005$) than in the control group (8/174, 4.6%).
- The **MTHFR C677T and MTRR A66G polymorphisms are significantly correlated** with the occurrence of spontaneous abortion.

Genet Mol Res. 2015 Jul 28;14(3):8500-8. PMID: 26345779

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MTHFR Increases Risk of Stroke 40%

- To investigate the possible associations between the MTHFR gene polymorphism and ischemic stroke, we performed a meta-analysis…
- Statistically significant association with ischemic stroke was identified for allele T polymorphism of MTHFR [fixed-effects OR=1.28, 95% confidence interval (95% CI): 1.17-1.40, P<0.00001] and marginally significant association was detected with genotype CT of MTHFR (fixed-effects OR=1.13, 95% CI: 1.01-127, P=0.04) and genotype TT of MTHFR (fixed-effects OR=1.43, 95% CI: 1.20-1.70, P<0.001).
- The results suggested that **the MTHFR C667T genetic polymorphism was significantly associated with increased risk of ischemic stroke.**

Gene. 2014 Feb 10;535(2):359-64. PMID: 24140489

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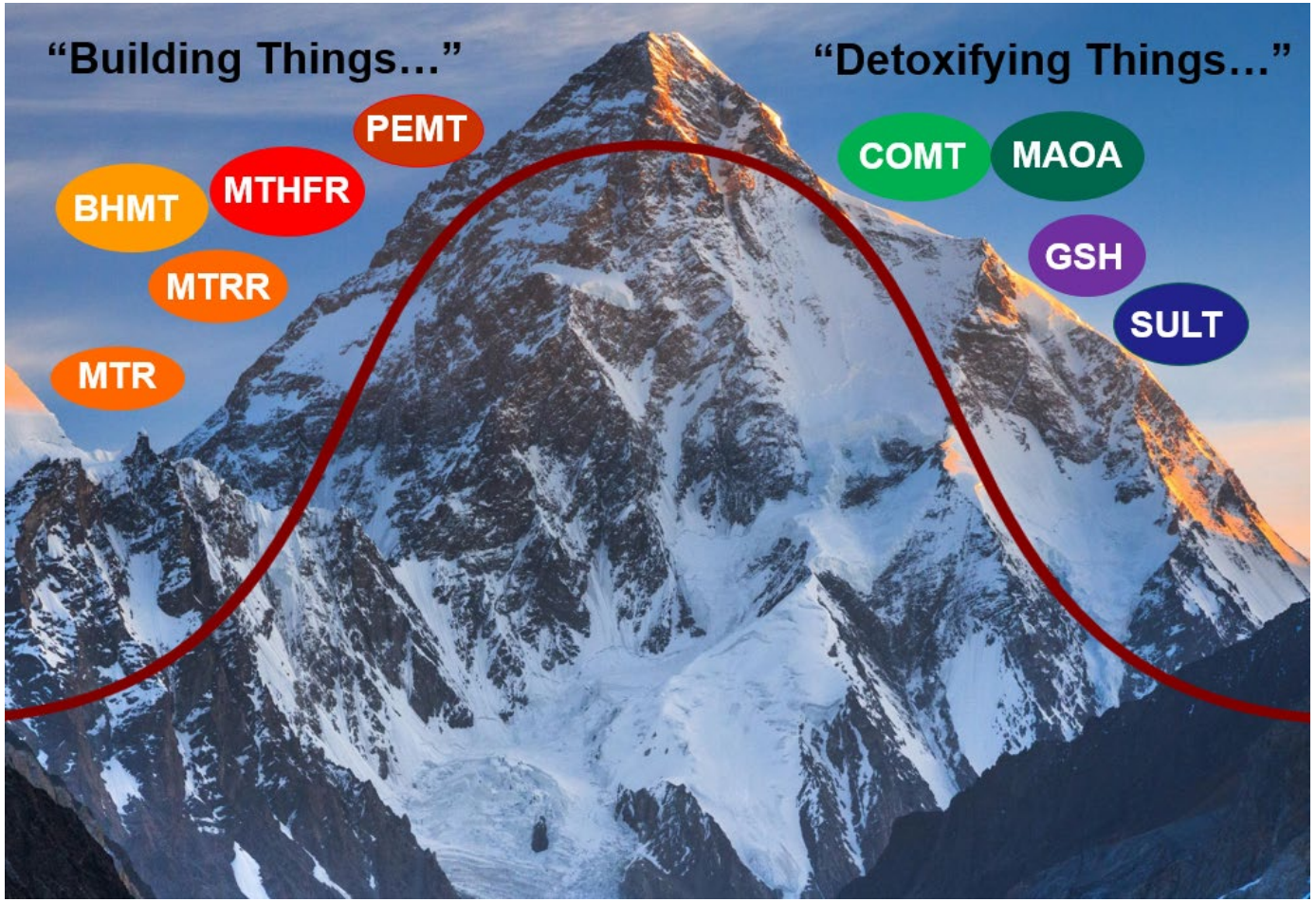
A Better Perspective of Methylation



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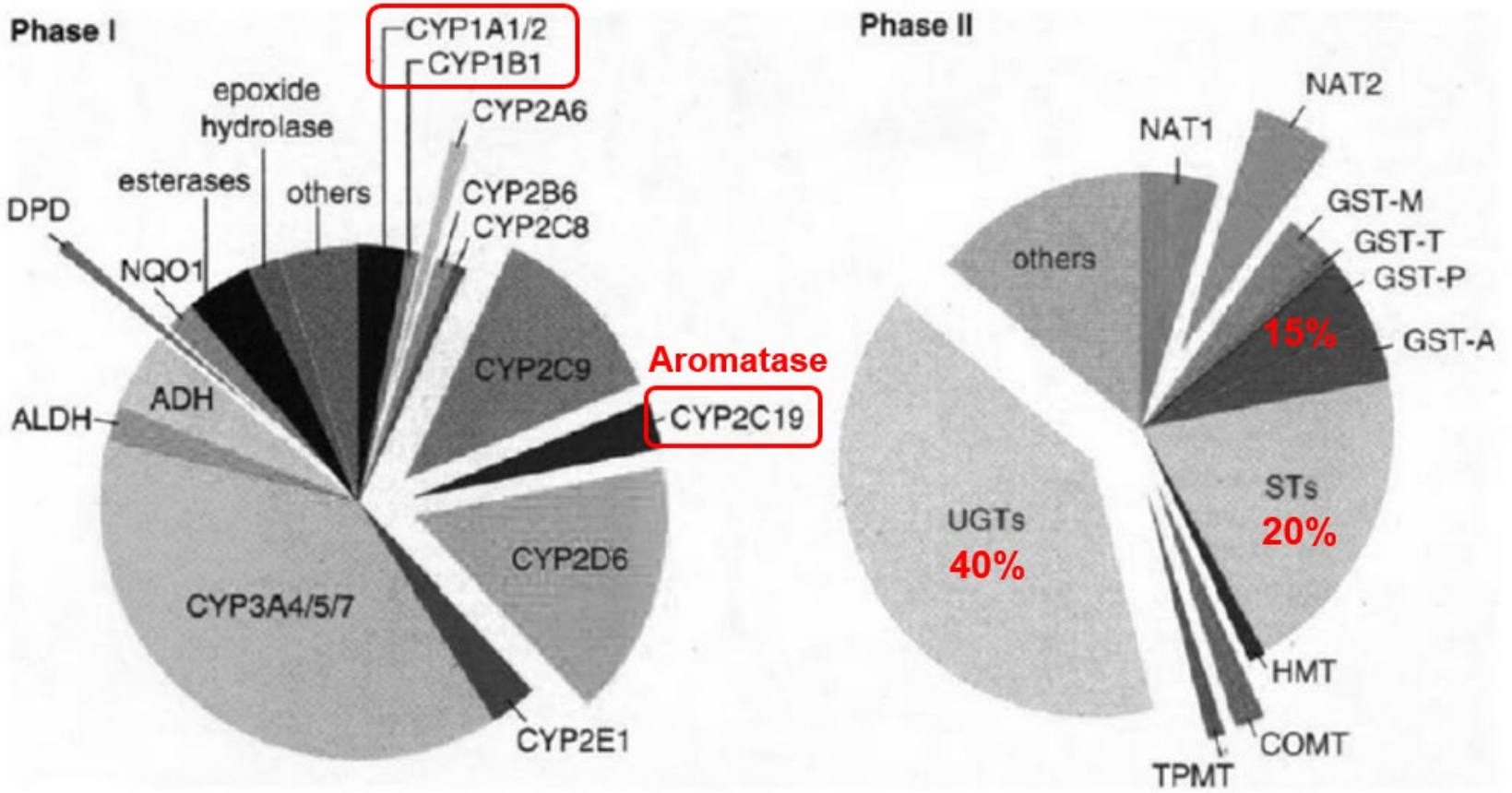
Phase 1 vs Phase 2 Distribution



Crit Rev Food Sci Nutr. 2016 Jul 29;56 Suppl 1:S95-S109. PMID: 26561312

Phase 2 Detox Pathways

Table 3. Major phase II detoxification activities in humans

Reaction	Enzyme	Localization[a]	Substrates
H_2O	Epoxide hydrolase	Microsomes Cytosol	Epoxides
Glutathione	Glutathione transferases	Microsomes	Electrophiles
Glucuronic acid (UDPGA)[b]	Glucuronyl transferases	Microsomes	Phenols, thiols, amines, Carboxylic acids
Sulfuric acid (PAPS)[b]	Sulfotransferase	Cytosol	Phenols, thiols, amines
Methyl Group (SAM)[b]	N- and O- methyl transferases	Cytosol Microsomes	Phenols, amines
Acetic acid (Acetyl-CoA)[b]	N-acetyl transferases	Cytosol	Amines
Amino acids (Acetyl-CoA, taurine, glycine)	Amino acid transferases	Microsomes	Carboxylic acids

[a] Microsome refers to membrane-associated activities but these activities may be localized to the cellular membrane or to internal membranes; cytosol refers to soluble activities present in the cytosolic portion of the cell

[b] Abbreviations in brackets are co-substrates: UDPGA = urindine - 3', 5' - diphosphoglucuronic acid; PAPS = 3' - phosphoadenosine 5' - phosphosulfate; SAM = S - adenosylmethionine; CoA = coenzyme A.

Data from Vermeulen.[4]

Hormones are *phenol* compounds and they are removed through these 3 main pathways…

Altern Med Rev. 1998 Jun;3(3):187-98. PMID: 9630736

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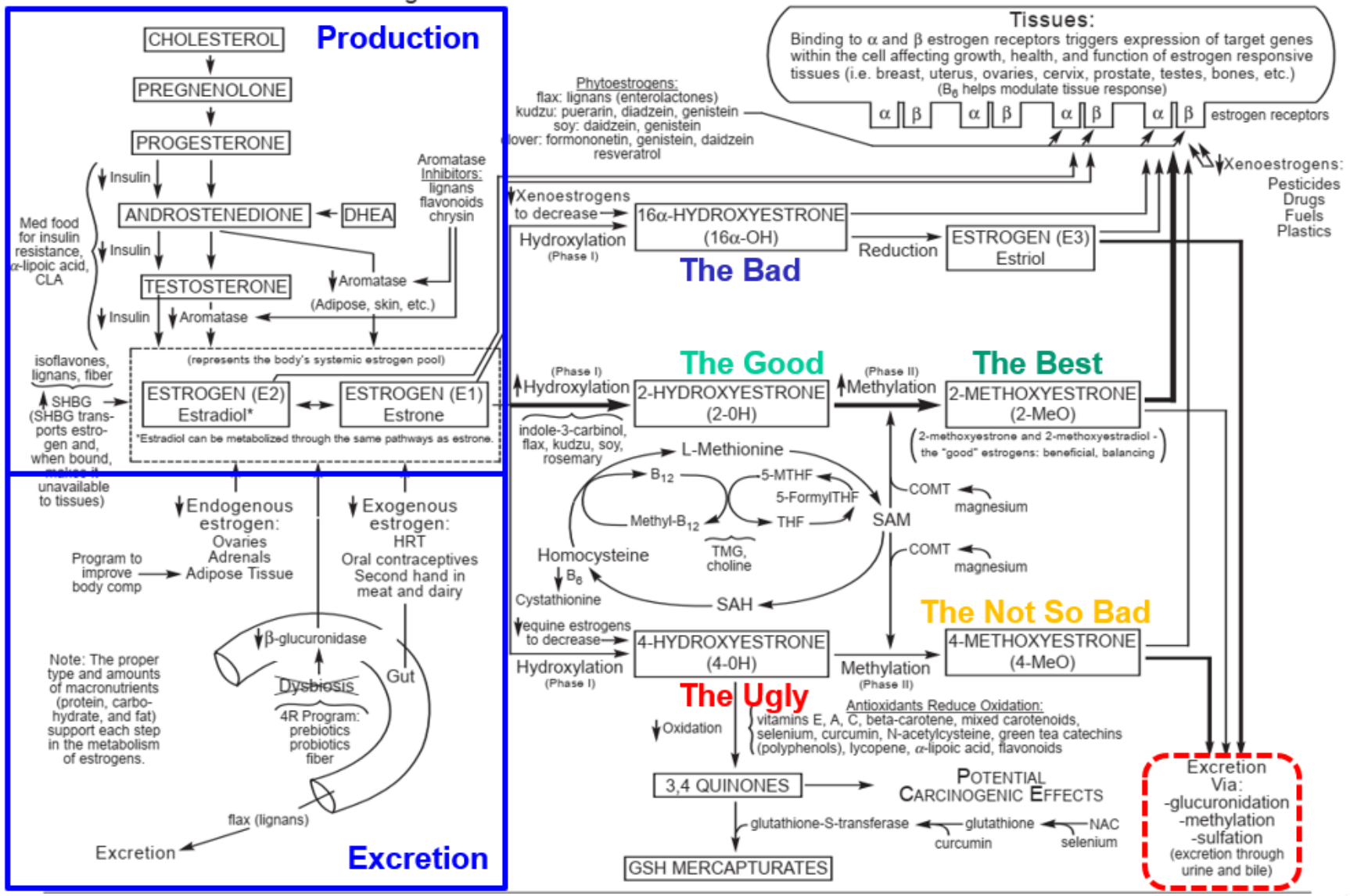
Figure 1.

Nutritional Influences on Estrogen Metabolism



HALL, DOUGLAS. (2001). Nutritional Influences on Estrogen Metabolism. Appl Nutr Sci Reports. 1.

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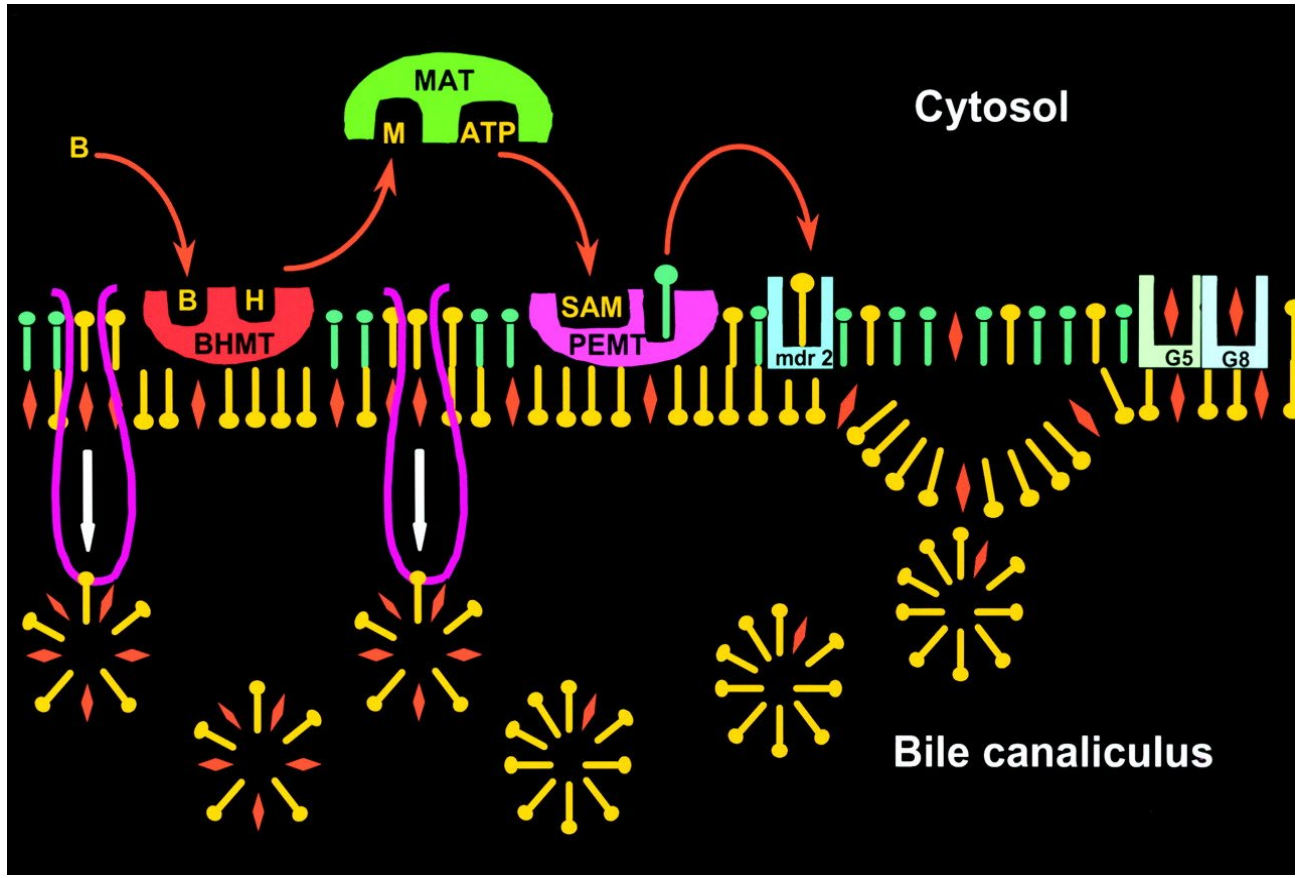
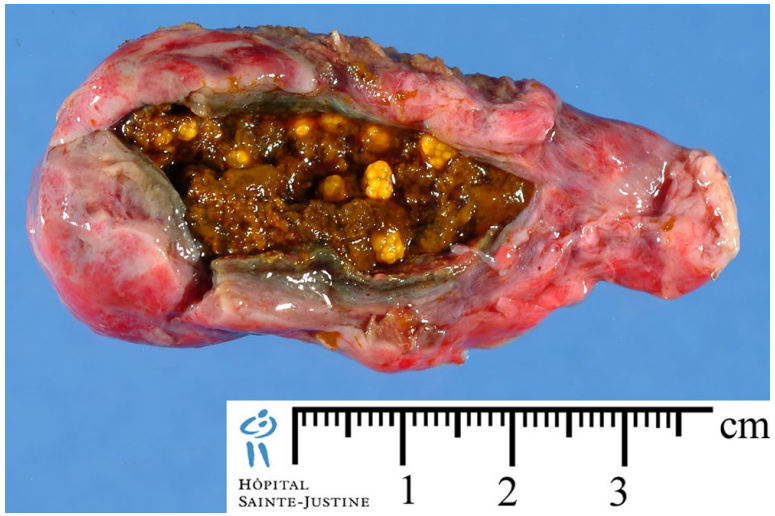
GB Function Methylation Dependent

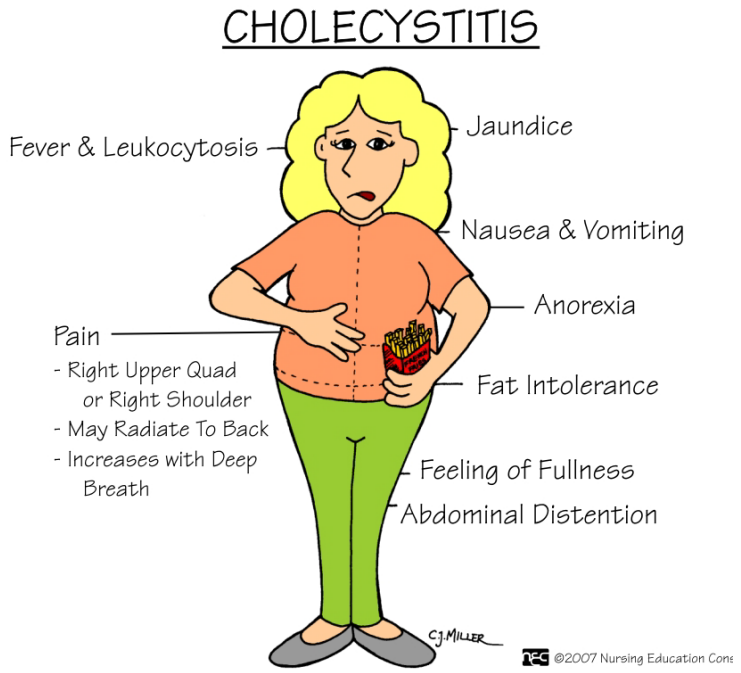


- We have shown that BHMT and PEMT, enzymes involved in the methylation of PE to PC, localized to canalicular membranes…and believe that local synthesis of PC, together with the presence of SR-BI, facilitates the excretion of cholesterol into the bile.

J Lipid Res. 2003 Sep;44(9):1605-13. PMID: 12810817

Excess Estrogen Causes GB Sludge





- **Estrogens and their metabolites are involved in pathogenesis of cholestasis diseases**, such as intrahepatic cholestasis of pregnancy (ICP), and cholestasis caused by postmenopausal hormone replacement therapy and administration of oral contraceptives.

Front Pharmacol. 2022 Jun 8;13:907271. PMID: 35754480

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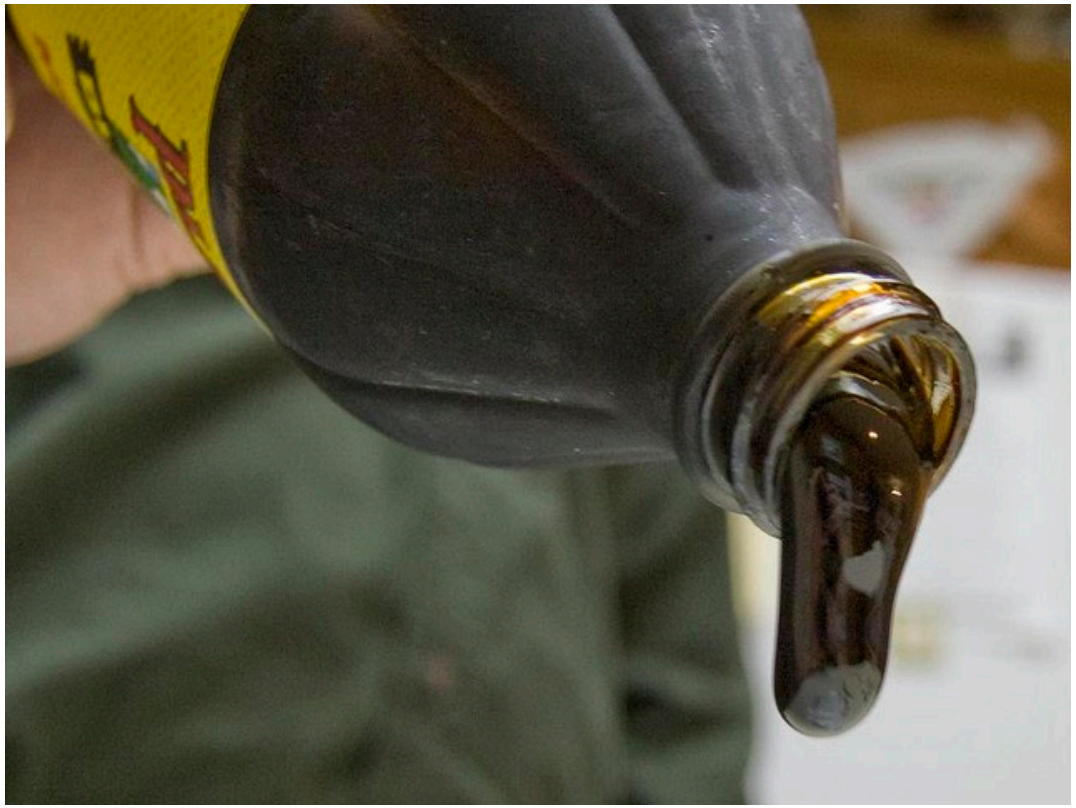
TUDCA (Taurine) and Methionine Reduce “SYRUP” Caused by Glucoronides



- Chronic liver disease induces an acquired deficiency of methionine adenosyltransferase, which catalyzes SAMe formation from methionine leading to a depletion of the amount of SAMe and potential **impairment of detoxifying processes** in the liver.
- Our previous experimental works demonstrated that simultaneous **treatment with UDCA and SAMe may exert beneficial, additive effect ameliorating cholestasis.**

J Gastrointestin Liver Dis. 2018 Sep;27(3):273-279 PMID: 30240471.

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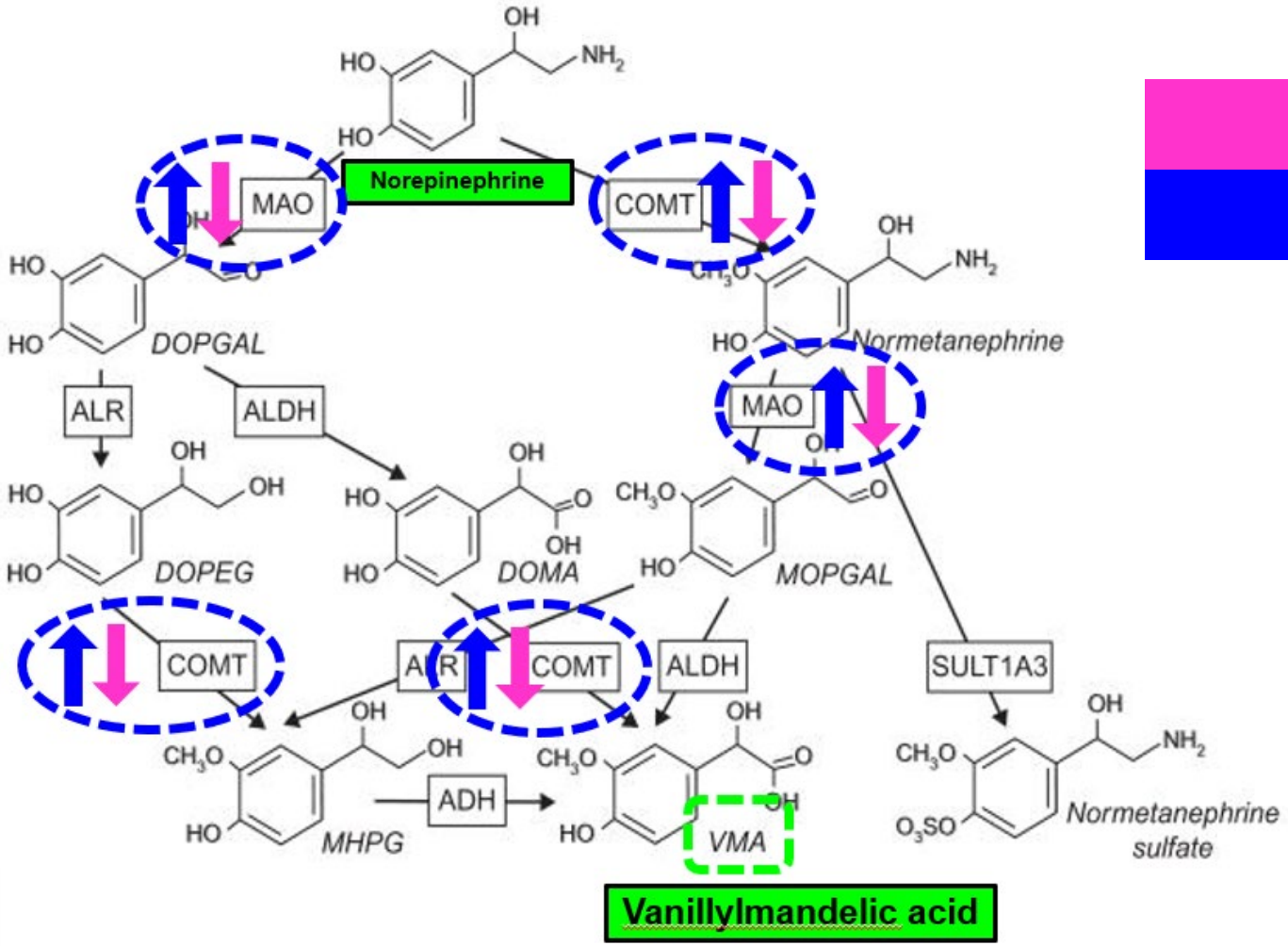
Gut, Epigenetics and Neurotransmitters



Estrogens

Testosterone

Int Rev Neurobiol. 2011; 100: 13–42. PMCID: PMC3371272

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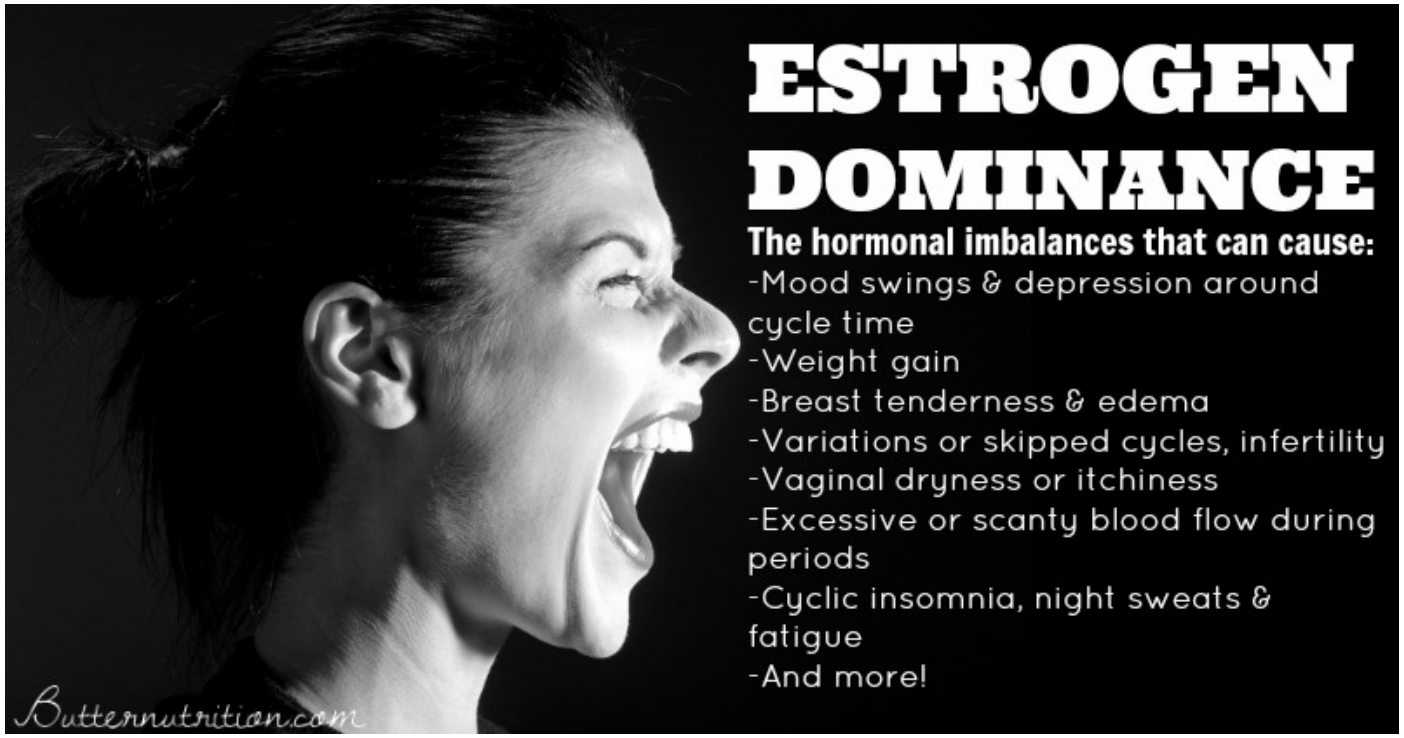
Estrogens INHIBIT MAO-A Brain Activity



- The present study provides strong evidence of a strict relationship between estrogen receptor and monoamine oxidase A activity in human cells of neural origin, thus favoring the hypothesis of **an antidepressive effect of estrogens** exerted via inhibition of the monoamine oxidative pathway.

Eur J Pharmacol. 1995 Sep 15;284(1-2):171-6. PMID: 8549621

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COMT Decreased 30% by Estrogen

- The COMT enzyme activity is reduced epigenetically by estrogen with 30% decrease in activity in females compared to males.
- **The Met158 carriers are more sensitive to stress and exhibit higher anxiety** and reactivity to lower levels of stress.

Sleep Med Rev. 2015 Aug;22:47-53. PMID: 25466290

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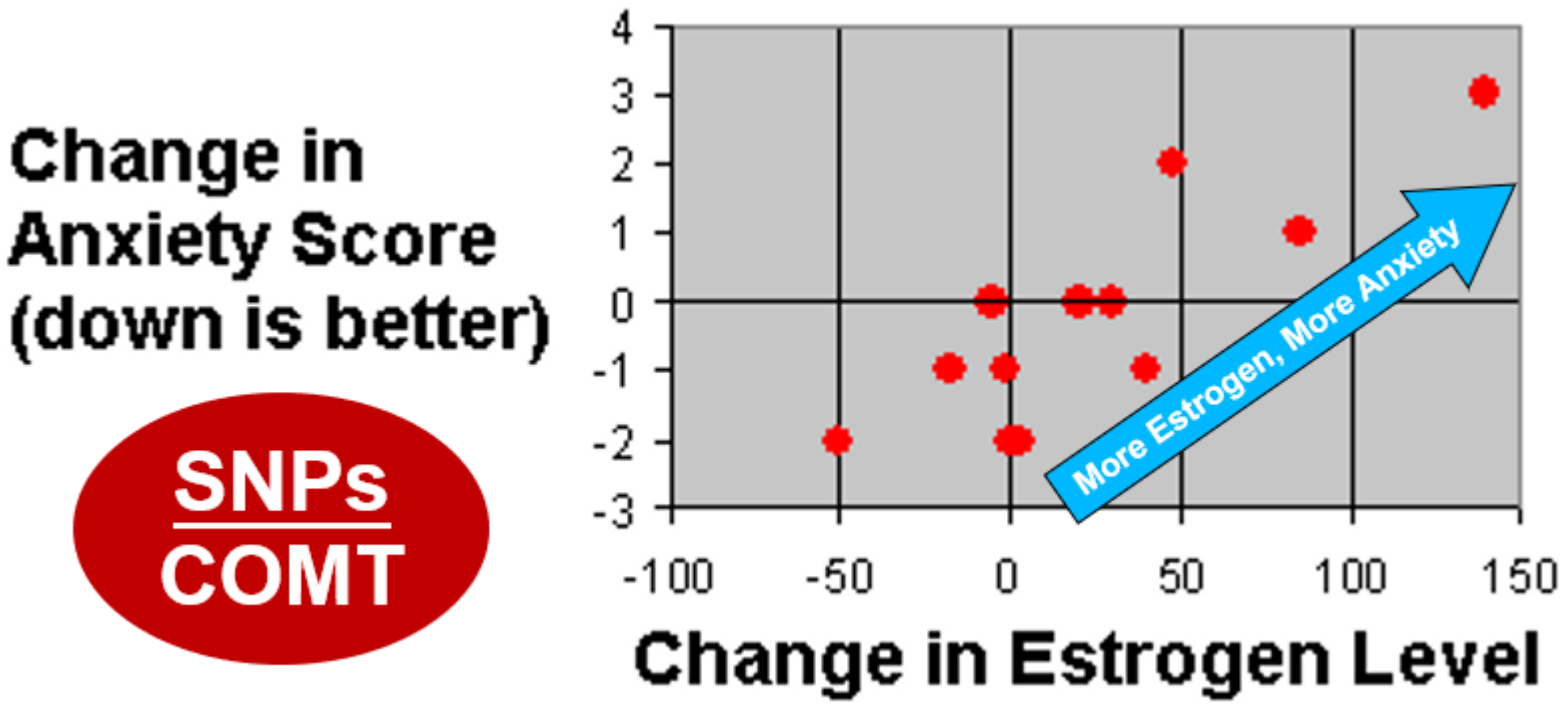
Estrogen Down-Regulates COMT



- We propose that E2 decreased COMT activity through down-regulation of its gene and protein expression mediated via ER interaction with response elements in the promoter region of the gene.
- Our findings may explain the **lower of COMT activity in women compared to that in men**, and, in part, the beneficial effects of E2 therapy in post-menopausal Parkinson's disease patients.

http://psycheducation.org/hormones-and-mood-introduction/basic-information-about-estrogen-in-psychiatry/

Neuropharmacology. 2003 Dec;45(7):1011-8. PMID: 14573393

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COMT +/+ Raises Anxiety, Lowers Heart Rate Variability

- We examined whether the COMT Val158Met variant could increase the risk of GAD through decreased resting parasympathetic nervous control in an age-specific manner…
- Our findings are the first to demonstrate that COMT Val158Met polymorphism is **associated with risk of GAD** via reduced resting parasympathetic nervous control, an age-specific risk pathway.

Psychoneuroendocrinology. 2019 Aug;106:57-64. PMID: 30954919.

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Catecholamine/Dopamine Bell Curve

Neurotransmitter or Receptor Deficiency

Low Catecholamine
- Food Cravings
- ADD/ADHD
- Addictions
- Substance abuse
- Anger
- Impulsivity
- High Risk Behavior
- Excessive Sleepiness

Optimum Neurotransmitter and Receptor Levels

Health is NOT found at the extremes

Neurotransmitter or Receptor Excess

High Catecholamine
- Schizophrenia
- Aggression/Violence
- Delirium
- Anxiety/Panic/Worry
- Tachycardia
- High BP
- Insomnia
- Paranoia
- Chronic Pain

** Dopamine deficiency can be relative, ie caused by low dopamine OR by normal dopamine levels and ELEVATED serotonin.

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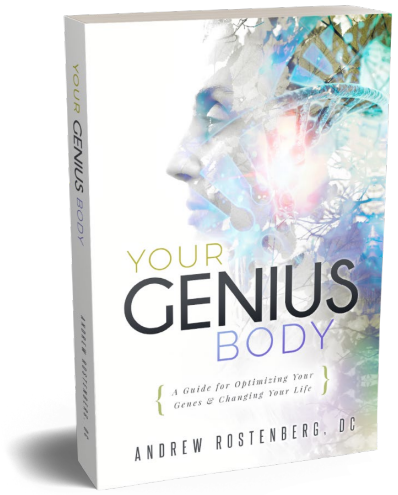
Join Us and Change More Lives



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