Nutritional Importance of Fats - Health and Disease

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Why worry about dietary fats and oils?

- By 2020, ~75% of all deaths;60% of all DALYs worldwide attributable to NCDs - cardiovascular diseases, type 2 diabetes, obesity, and cancers.
- Largest increases and burdens in low and middle income countries rather than in high income countries.
- Most burdens occur prematurely, can be prevented or delayed.
- Diet one of the fundamental risk factors for health, disease, and disability in the world.
- Eight of the top 20 individual causes of disease burden worldwide due to poor nutrition

Reconstructed Paleolithic diets

- East Africa:
- ranges of nutrient intakes on which humans evolved.
- Range of medians in energy %) intakes :
  - moderate-to-high protein(25%–29%),
  - moderate-to-high fat (30%–39%) and
  - moderate carbohydrates (39%–40%)

Omega-6/Omega-3 Ratios in Different Populations

Population	ω-6/ω-3
Paleolithic	0.79
Greece prior to 1960	1.00–2.00
Current Japan	4.00
Current India, rural	5–6.1
Current UK and northern Europe	15.00
Current US	16.74
Current India, urban	38–50

Genetic variation in fatty acid biosynthesis

- Genome-wide genotyping (n = 5652 individuals) of the FADS region in 5 European population cohorts - [FADS1 and FADS2, encode rate-limiting enzymes for fatty acid metabolism]

- analyzed available genomic data from human populations, archaic hominins, and more distant primates

- present-day humans have two common FADS -- haplotypes A and D that differ dramatically in their ability to generate long-chain polyunsaturated fatty acids (LC-PUFAs).

Haplotype D– most common

Associated with high blood lipid levels

- Enhanced ability to produce AA and EPA from precursors LA and ALA - specific to humans
- appeared after split of the common ancestor of humans and Neanderthals
- shows evidence of positive selection in African populations in which it is presently almost fixed
- Efficient synthesis of LC-PUFAs from Linoleic acid

Haplotype A – less common

Associated with low blood lipid levels

- associated with low blood lipid levels.

Haplotype D represents a risk factor for coronary heart disease (CHD), cancer, obesity, diabetes and metabolic syndrome

Genetic variants in FADS cluster

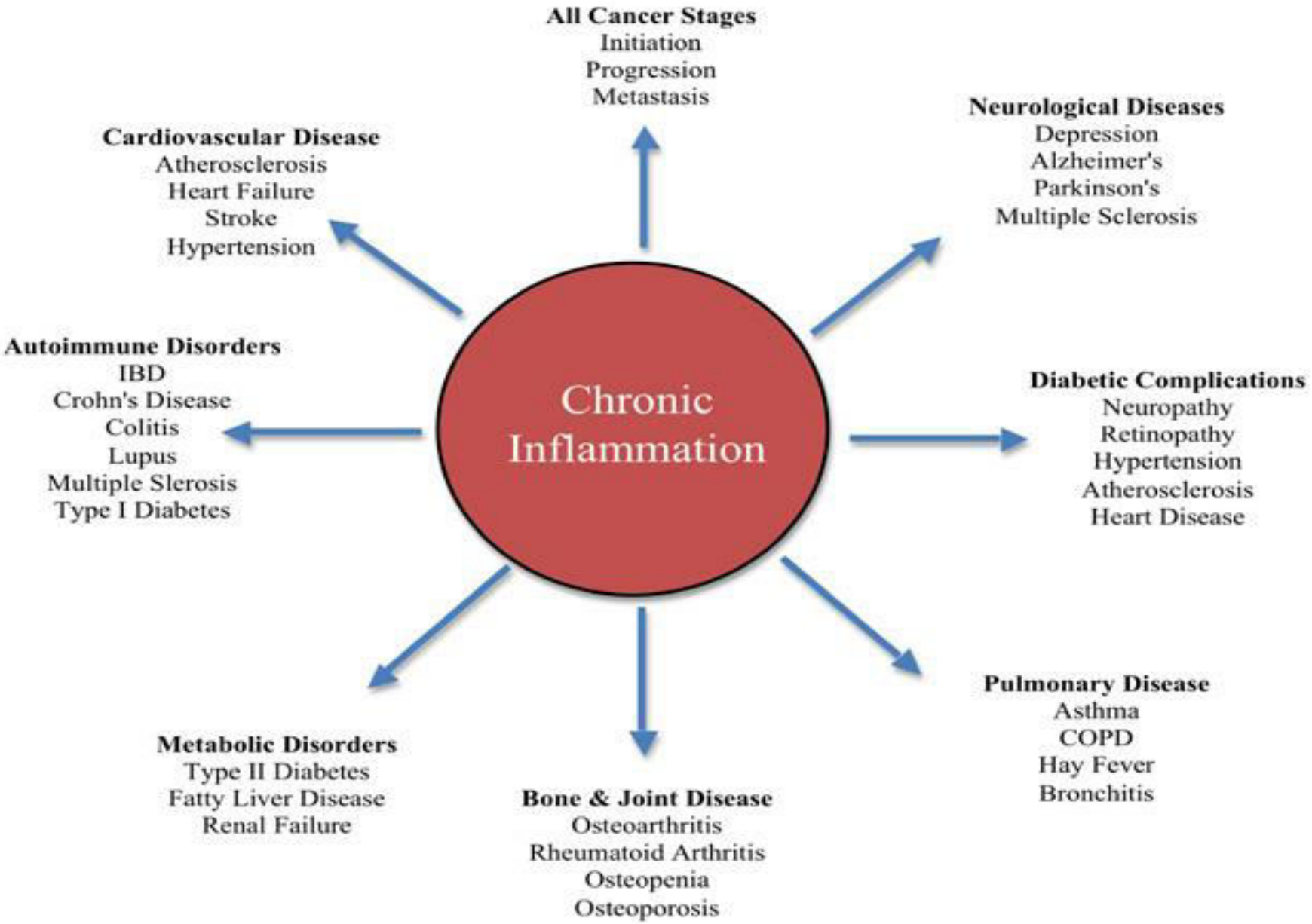
- determinants of long-chain PUFA levels in circulation, cells and tissues.
- genetic variants have been studied in terms of ancestry, evidence is robust relative to ethnicity.
- 80% of African Americans and about 45% of European Americans carry two copies of the alleles associated with increased levels of AA.
- FADS2 the limiting enzyme , some evidence that it decreases with age.
- Premature infants, hypertensive individuals, and some diabetics have limited ability to make EPA and DHA from ALA.
- Needs to be considered when making dietary recommendations

Inflammation and Disease

- Inflammation an essential component of the innate immune response to tissue injury.

- Movement of serum proteins, lipids, and blood leukocytes into affected tissues eliminate or neutralize the source of tissue injury then restore normal tissue structure and function.

- Failure to control the magnitude & duration of inflammatory response can damage host tissues and contribute to pathology, independent of original insult.


All Cancer Stages
Initiation
Progression
Metastasis
Neurological Diseases
Depression
Alzheimer's
Parkinson's
Multiple Sclerosis
Cardiovascular Disease
Atherosclerosis
Heart Failure
Stroke
Hypertension
Autoimmune Disorders
IBD
Crohn's Disease
Colitis
Lupus
Multiple Slerosis
Type I Diabetes
Chronic Inflammation
Diabetic Complications
Neuropathy
Retinopathy
Hypertension
Atherosclerosis
Heart Disease
Metabolic Disorders
Type II Diabetes
Fatty Liver Disease
Renal Failure
Bone & Joint Disease
Osteoarthritis
Rheumatoid Arthritis
Osteopenia
Osteoporosis
Pulmonary Disease
Asthma
COPD
Hay Fever
Bronchitis

Dietary Fats and Fatty Acids

- **Current concerns**: SFA, MUFA, PUFA, Trans fats, Dairy fats,

- Specific dietary lipids can individually influence :
- structural composition of cells
- Fluidity of cell membranes(PUFA enhance membrane fluidity
- signalling functions of specific cellular processes.
- metabolic pathways,
- tissue fatty acid composition which is linked with changes in tissue function

Importance of Membrane Fluidity

- Influence CHD risk through multiple pathways:
  - modulate the activity of proteins involved in ion transport
  - Signal transduction,
  - cell Ca2+ handling,
  - intracellular pH regulation
- decreased membrane fluidity may play imp role in pathogenesis of hypertension
- Could significantly alter the vascular endothelial response to shear stress
- Impair endothelial cell wound closure
- interfere the sodium-dependent D-glucose transport --- insulin sensitivity

Saturated Fatty Acids

- Hypercholesterolemic
- Myristic acid the most potent SFA while stearic acid apparently neutral.
- Rodents - high fat diet --- impaired insulin sensitivity in liver, skeletal muscle, liver.
- Dietary SFA significantly increased risk of CHD primarily increased plasma LDL-cholesterol.
- Replacement of SFA with PUFA in the diet significantly reduced LDL-cholesterol concentration and CHD risk.
- A high SFA and low PUFA diet raises CHD risk through promoting thromboembolism

Cis-Monounsaturated Fatty Acids

- Worldwide, mean intake ranges varies from 3.5 % of total energy in certain regions of China to ~ 22 % in Greece.
- Oleic acid (18:1; n-9) the predominant *cis* - MUFA, accounts for > 92 % of all MUFAs consumed.
- Favourable effect on serum lipoprotein profile.

Substitution of high SFA fats/oils with oils rich in cis-MUFA

- Significant decreases in :
- Serum Total cholesterol, LDL-cholesterol, apoB100, total to HDL cholesterol ratio.
- Little change in Serum HDL-cholesterol, apo-AI, and triacylglycerol
- PUFA effect slightly more favourable than MUFA, esp on LDL and total to HDL-cholesterol ratio.

- **An oil rich in cis-MUFA and DHA, however, increased LDL-cholesterol and HDL cholesterol,** although it lowered serum TAG as compared with four other oils -olive oil, high-oleic acid sunflower oil, high oleic acid safflower oil, and rapeseed oil.

- Replacing dietary SFAs with cis-MUFAs did not affect:
  - Fasting flow-mediated vasodilation (FMD) of the brachial artery
  - Arterial stiffness,
  - Endothelial activity but
  - Night systolic blood pressure reduced by 4.9 mm of Hg

Replacement of SFA by carbohydrates from refined starches/added sugars may not decrease CHD risk, while replacement by carbohydrates from whole grains or cis-polyunsaturated fatty acid (cis-PUFA) does.

Postprandial Vascular Function

- Responses compared between 18 normal-weight and 18 obese men following three isocaloric high-fat challenges differing in fatty-acid composition.
- In random order, provided a milkshake containing 95 g of fat,
- Either high in SFAs/cis-MUFAs/ n-3 long chain PUFAs.
- Compared with SFA and n-3 PUFA shakes, cis-MUFA milkshake ---- more pronounced decrease in blood pressure and the augmentation index —a measure of the arterial pressure wave form that depends on the tone of peripheral resistance arteries.

Energy Intake

- 15 healthy normal-weight subjects
- In random order given 30 mL of high-oleic acid sunflower oil/virgin olive oil/ sunflower oil plus 30 g of bread.
- After consumption of oleic acid-rich oils rich, energy intake at the subsequent self-chosen lunch reduced,

- Possibly related to increased post prandial conc of Oleoylethanolamide, a compound produced by the small intestine and involved in appetite regulation.

Thermogenesis, Fat Oxidation

- Acute-meal studies: possibly increased diet-induced thermogenesis and fat oxidation with high unsaturated fat diets as compared with SFA-rich diets.
- No differences between MUFA and PUFA.
- MUFA-rich diets may induce greater energy expenditure, diet-induced thermogenesis or fat oxidation than SFA-rich diets
- Inconsistent results with peanut diets

PREDIMED TRIAL

- Prospective trial between 2003 -2012:
- Higher cis-MUFA intakes : inverse associatn with CVD, cardiovascular death, and all-cause death.

- Isocaloric substitution of 5 % of energy from SFAs or trans-FAs with cis-MUFAs --- 37 and 40 % lower risk of total CVD events.

- Similar trends in **Nurses Health Study** (1980–2010; 84,628 US women) and the **Health Professional Follow-Up Study** (1986–2010; 42,908 US men)

- Replacing 5 % of energy from dietary SFA with equivalent amount of cis-MUFA associated with 15% lower CHD risk.

Trans fatty acids

- Increased risk of CHD via its adverse effects on blood lipids --- increased LDL-C, TC,Apo B levels,
- Decreases HDL-C and ApoA levels.

- Meta-analyses of prospective cohort studies -- incidence of coronary heart disease increased by 27% when 2 Energy% of MUFA in diets replaced by industrially produced TFA

Trans fats and Fetal Growth

- TFAs in maternal diets of transferred to fetus through placenta.

- May block PUFAs transfer to fetus or interfere with PUFA metabolism.
- May also prevent desaturation of α-linolenic acid to DHA and of linoleic acid to arachidonic acid, thereby influencing fetal growth.

Trans fatty acids contd

- Elaidic acid one of the main isomers
- EA induces de-novo synthesis of all four major lipids -- fatty acids, cholesterol, cholesteryl esters and triglycerides
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- Possibly through modulating lipogenic gene expression -
- Increase in cholesterol synthesis through significant up regulation of essentially all proteins involved .
- Expression of proteins involved in FA synthesis, activation and esterification to cholesterol also increased.
- Several proteins regulated as a means to export newly synthesized cholesterol and FA.

Dairy Fatty Acids

- Epidemiological studies suggest beneficial effects of low-fat dairy consumption (***recommended in DASH diet***) on hypertension and stroke.
- Whole-fat dairy discouraged due to potential adverse effects of saturated fat on CHD.
- Recent meta-analysis -- included >250 000 participants in 6 prospective observational studies:
- No evidence of harmful associations between self-reported overall milk consumption and incidence of CHD/stroke

Dairy Fats: trans-16:1n27 an established biomarker for high-fat dairy product intake

- **trans-16:1n27** :Lowers hepatic fat content and therefore
- Improves hepatic insulin sensitivity and glucose tolerance

- May stimulate fat oxidation or inhibit de novo lipogenesis in the liver

- **Phytanic acid**: a minor constituent -- potent agonist of peroxisome proliferator–activated receptor —a liver transcription factor -- important role in regulating liver fat oxidation

- May acts synergistically with trans-16:1n27 (& other fatty acids)to stimulate hepatic β-oxidation and/or inhibit de novo lipogenesis

Dairy fats –humans

- In men, dairy fat intake inversely associated with metabolic anomalies eg elevated fasting plasma glucose concentrations.

- Among young adults who were overweight at baseline (but not among leaner individuals), dairy consumption inversely related to incidence of metabolic factors associated with insulin resistance.

- In the Health Professionals Follow-up Study, dietary pattern characterized by higher dairy intake, especially low-fat dairy intake, related to a reduced risk of type 2 diabetes in men.

- A dietary pattern rich in low-fat dairy products has also been associated with lower riskof type 2 diabetes in middle-aged or older women

Omega-6/Omega-3 Fatty Acid Ratio

- **During evolution** in humans - ratio was **1:1**
- In Western diets **today** -- the ratio is **20:1**
- Eicosanoid products derived from n-6 PUFAs eg PG E2, LT B4 synthesized from arachidonic acid (ARA) --- more potent mediators of thrombosis and inflammation than similar products derived from n-3 PUFAs (PGE3 and LTB5 synthesized from eicosapentaenoic acid (EPA).
- Unbalanced omega-6/omega-3 ratio in favor of omega-6 PUFAs - highly prothrombotic and proinflammatory
- Contributes to the prevalence of atherosclerosis, obesity, and diabetes.

A diet rich in n-6 fatty acids shifts the physiological state to one that is proinflammatory, prothrombotic, and proaggregatory, with increases in blood viscosity, vasospasm, vasoconstriction andcell proliferation.

- rapid dietary changes over short periods of time as have occurred over the past100–150 years is a totally new phenomenon in human evolution.

- Modern agriculture, by changing animal feeds as a result of its emphasis on production, has decreased the omega-3 fatty acid content in many foods: animal meats, eggs, and even fish.

N-6 PUFA and Obesity/Adiposity

- n-6 PUFA rich diets can increase abdominal adiposity possibly stimulating lipogenic pathways.
- Perinatal exposure of mice to high n-6 fatty acid diet (similar to Western diet) ⇒ progressive accumulation of body fat across generations,
- Human studies AA level in adipose tissue associated with BMI, overweight status of children.
- High n-6/n3 fatty acids in umbilical cord RBC membrane phospholipids associated with high subscapular skin-fold thickness at 3 years of age.

N-6: n-3 ratios

- **Experimental studies** --- n-3 and n-6 fatty acids elicit divergent effects on body fat gain through :
- adipogenesis, lipid homeostasis , systemic inflammation ,brain-gut-adipose tissue axis , inflammatory properties of downstream eicosanoids, which ultimately affect pre-adipocyte differentiation and fat mass growth

- Metabolites of ARA (20:4n-6) play important roles in:
- terminal differentiation of pre-adipocyte to mature adipocyte [inhibited by n-3 fatty acids at multiple steps]-- alterrates of adipocyte differentiation and proliferation
- N-6 fatty acids increase cellular triglyceride content by increasing membrane permeability, whereas n-3 fatty acids reduce fat deposition in adipose tissues by suppressing lipogenic enzymes and increasing β-oxidation .
- AA metabolites prostaglandins E2 and F2 have inhibitory role in browning process of white fat cells --converted into energy-dissipating brown fat cells which probably play a role in controlling energy balance by lowering body weight.

N-6 &Weight Gain, Insulin resistance

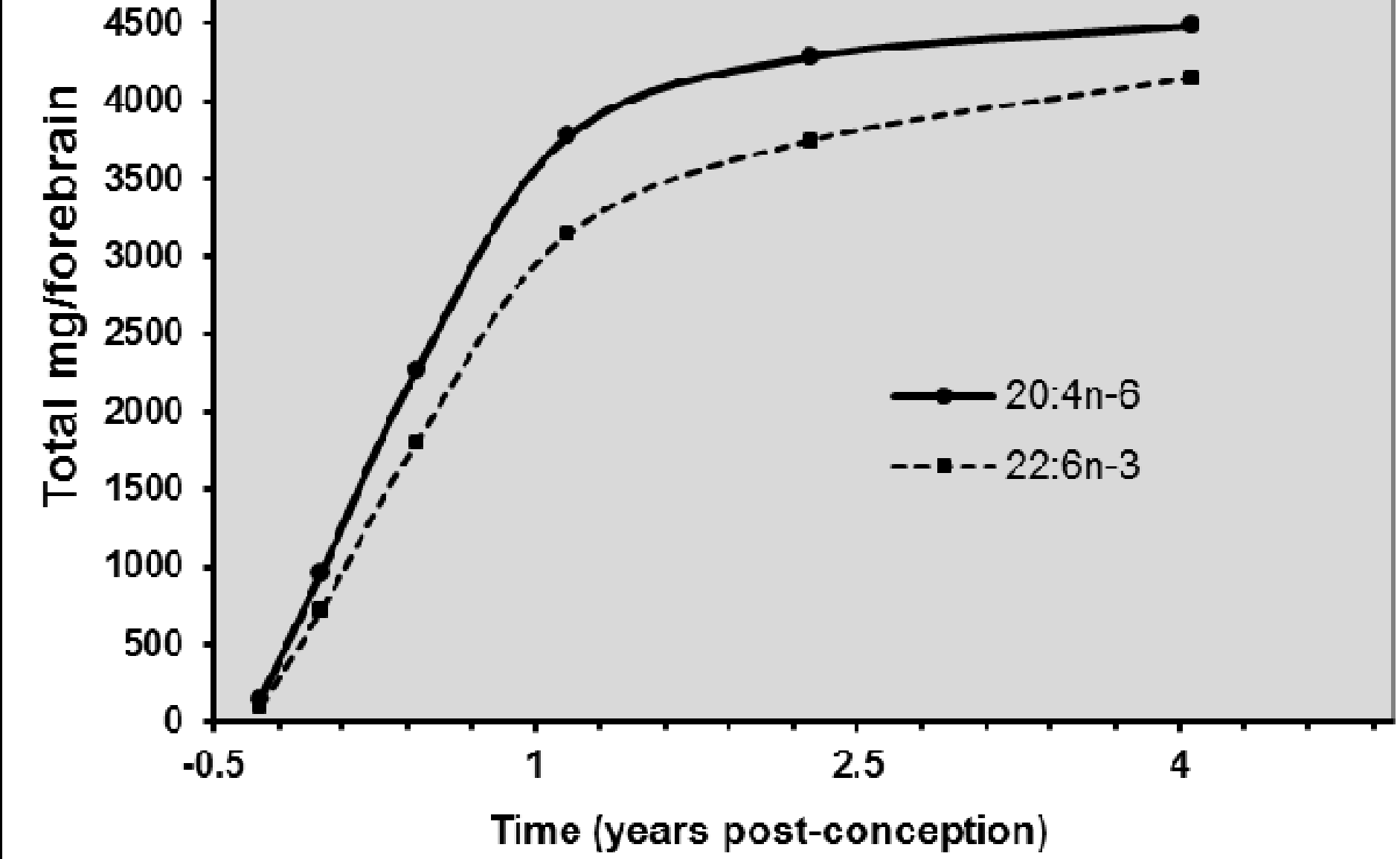
- Increasing precursor pool of AA causes excessive endocannabinoid signaling leading to weight gain &a metabolic profile associated with obesity.

- Endocannabinoids activate endogenous cannabinoidCB1 ,CB2 receptors in brain, liver, adipose tissue, gi tract .

- This system functions in concert with other systems regulating food intake & energy balance, regulated by leptin, insulin, ghrelin, cholecystokinin, and other signals.

- .Activationof CB1 receptors in hypothalamus leads to increased appetite and food intake.
- Mice -- endocannabinoids selectively enhance sweet taste, could stimulate food intake in present scenario – availability of sweet foods??
- Animals -- high n-6 acid intake -- decreased insulin sensitivity in muscle, promotes fat accumulation in adipose tissue.

- High n-6 fatty acids increase leptin resistance and insulin resistance



ARA indispensable for brain growth -- important role in cell division and signaling

Arachidonic Acid- Brain growth & neural development

- Mammalian brain -60% fat - little variation in DHA and ARA (25%)composition of brain across species
- ARA -- mediates neuronal firing, signalling, long-term potentiation maintains hippocampal plasticity, defends hippocampus against oxidative stress by activating PPARγ.

- Immediate precursor for Adrenic acid – 3rd most abundant PUFA in the brain, in large quantities in myelin lipids, particularly phosphatidylethanolamine – needed for neural tissue development

- Activates syntaxin-3 a plasma membrane protein involved in the growth and repair of neurites – growth of neurites critical step in neuronal development

Other functions of ARA

- Eicosanoids from ARA both **pro and anti –inflammatory**
- **Infant and childhood growth** -- hormonal regulation of normal bone formation and whole body mineral metabolism -- mediates vitamin D3-regulated chondrocyte maturation & proliferation for mineralization of skeletal growth plates.
- Cardiac muscle tissue – concs 2-3X > skeletal tissue. Critical for muscle contraction.
- Cooperative role with myo-inositol 1,4,5-triphosphate (IP3) in glucose-induced calcium mobilization and insulin secretion by pancreatic islets.
- Infants with lowest birthweights have lowest levels of ARA.
- There appears to be a tightly regulated synergism between DHA and ARA at low DHA status and an antagonism at high DHA status.
- Vulnerable – new born infants of diabetic mothers – low LCPUFA status-- impaired and altered sensory-cognitive and psychomotor functions at birth and reduced visual and memory performance at 8 and 12 months

- Deficits of ARA and DHA may contribute to the complications related to prematurity.
- LCPUFA supplementation (ARA &DHA) significantly delayed time to first allergic illness and skin allergic illness.
- Reduced vascular or endothelial integrity leads to hemorrhage or ischemia.
- ARA acts as an endothelial relaxation factor and plays a dominant role in endothelial membrane lipids.

Relationship of dietary fat and microbiome

- High fat diet== animal models ⇒ changes in gut microbiota & intestinal permeability to endotoxin
- Promotes post prandial entry of insoluble fraction of lipopolysaccharide ⇒ inflammation.

- SFA may modify structure and function of gut microbiota
- Sufficient to induce obesity and IR
- Mice: Diet rich in n-6 resulted in dysbiosis, bacterial overgrowth, bacterial invasion of intestinal epithelial cell layer.
- Excess dietary N-6 PUFAs caused higher adipose expression of resistin, a hormone linked with inflammation and IR, than after consumption of saturated fat.
- Prevented by fish oil (DHA+EPA)-- reversed bacterial overgrowth and reduced fattydiet-induced inflammation
- Monounsaturated fatty acids antagonize dysbiosis and promote insulin sensitivity

- ***In summary***:
- Replacing SFAs with PUFAs associated with cardiovascular benefit
- Epidemiological studies support a beneficial association of ω-3 fatty acids with CVD; however, clinical trial studies to date have not consistently confirmed this.
- Replacement of SFAs with CHOs has not been associated with benefit and may be associated with increased CVD risk.
- There is growing evidence that SFAs in the context of dairy foods, particularly fermented dairy products, have neutral or inverse associations with CVD.
- Accumulating evidence food sources of SFAs can vary in their associations with CVD risk independent of their SFA content. This is likely due to components within foods other than SFAs that may singly / synergistically affect development and progression of CVD.
- Therefore, the SFA content of foods is not necessarily a useful criterion on which to base food choices.
- Overall dietary patterns that emphasize vegetables, fish, nuts, and whole versus processed grains are the mainstays of heart-healthy eating and for achieving and maintaining cardiovascular health.

Thank you