

The Ageing Brain: Influences of *in utero* and early childhood nutrition on later neurocognition



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Nutrition and Dementia

- WHO (2012) estimates that worldwide 35.6 million people live with dementia
 - Alzheimer's disease (AD) is the most common form
- Nutrition and lifestyle factors modify risk, incl.
 - Weight control (*BMJ. Jun 11, 2005; 330(7504): 1360*)
 - ↑ intakes of **fruits and vegetables, fatty fish,(not fried) and omega-3 rich oils** (*Curr Gerontol Geriatr Res. 2012; 2012: 926082*)
 - ↑ **intakes of antioxidants** (*Genes Nutr. 2014;9(2):382*)
 - **↑B-vitamins and ↓homocysteine** (*J Physiol Pharmacol. 2014;65(1):15-23*)

Rising Tide: The Impact of Dementia on Canadian Society

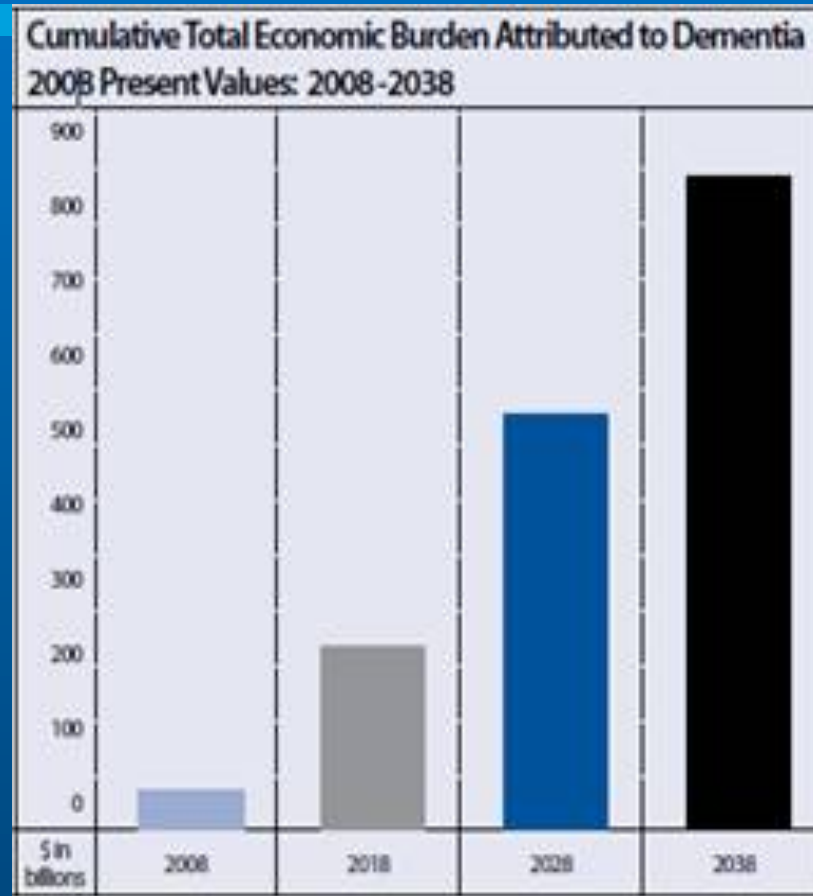
http://geriatricresearch.medicine.dal.ca/rising_tide.htm

- The Alzheimer's Society of Canada warns of a growing dementia epidemic
 - Will **overwhelm healthcare and devastate the Canadian economy in one generation**
 - Currently **no effective treatments**
- Preventative measures are recommended
 - 50% **increase in exercise**
 - Programmes to **promote healthy diet and lifestyle choices**

Rising Tide: The Impact of Dementia on Canadian Society

“By far, the most effective is the plan to promote healthy diet and lifestyle choices to delay dementia onset.”

Rising Tide: The Impact of Dementia in Canada
Alzheimer's Society of Canada 2010



Pregnancy: the roots of chronic diseases of ageing?

The Barker Hypothesis

– a historical perspective –

- 1950s: Generally believed that the fetus was protected from nutritional harm
 - The Mother would pay the nutritional price of the pregnancy; rarely the child
- 1990s: David Barker MD, PhD proposes that maternal diets unbalanced in macronutrients or deficient in micronutrients
 - Will fail to match fetal nutrient demands, and set the stage for chronic disease in adult life

The Barker Hypothesis

– proof of principle –

- Proof of principle comes from studying **birth records of those *in utero* during famines** (Sweden, Holland) and wartime (WW2)
 - Studies also seek **evidence for trans-generational effects**
- **Birth weight used as a surrogate for *in utero* malnutrition**
 - For most available studies, there are **few direct measures of actual maternal nutrient intakes**

Ethel Margaret Burnside

- In the early 20th C there was widespread concern about the physical deterioration of the British people
- Ethel Margaret Burnside was appointed Hertfordshire's first Chief Health Visitor and Lady Inspector of Midwives
 - charged with improving childrens' health in Hertfordshire



The Hertfordshire Cohort

1911-1948

- A midwife **attended all women during childbirth**
 - recorded the birth weight on a card
- A health visitor **went to each baby's home throughout its infancy**
 - Recorded **illnesses, development, and method of feeding**. Baby was re-weighed at 1 year of age
- Information was transcribed into ledgers at the Hertfordshire county office

Extract from the Hertfordshire ledgers kept by midwives from 1911 – 1948

Weight at Birth.	Weight 1st Year	Food.	No. of Visits.	Condition, and Remarks of Health Visitor.			
				W	V	D	T
8 $\frac{1}{4}$ lbs	24 $\frac{1}{2}$ lbs	B.	11	Y	-	-	4
Healthy & well developed.				Buckland School. Card to S.			
7 lbs	18 $\frac{1}{4}$ lbs	B	12	h.	Y.	Y.	8
moved to Bury Green Dr. Hadham.				Had measles, pneumonia.			
8	20	Bot.	11	Y.	Y.	?	4
I.B. scar on neck opened. Ant. fontanelle still open 23 yrs. Abdomen very large & prot.							
8 $\frac{1}{2}$	22	B.B.	9	Y	Y	Y	10
Healthy & normal.				Buckland School. Card.			

The Hertfordshire Cohort Today

- 15,000 subjects born in Hertfordshire before 1940 and still currently living there
 - Recruited for on-going research
- Findings so far: Newborn term infant $\leq 5\text{lbs}$, or who gained weight slowly had \uparrow risk of later life
 - CVD, Insulin Resistance, Type II Diabetes
 - Osteoporosis and sarcopenia
- To date, too few subjects have developed dementia to draw conclusions

Links between childhood cognition and later life dementia

IQ in Childhood and Cognition in Old Age

- Higher childhood IQ now linked to **preservation of cortical thickness in old age** (*Mol Psychiatry*. 2013 Jun 4. Epub ahead of print)
- Cognitive ability at age 11 years can predict late life cognitive ability (*Neurobiol Aging*. 2013 Dec;34(12): 2740-7)
 - Early-life IQ moderates later life **development of cortical white matter hyperintensities (WMH)**
 - Increased numbers of **WMHs are a risk for dementia**

Infant Brain Development and Maternal Nutrition

Nutrition in Pregnancy and Offspring IQ

- **Unsaturated fatty acids (esp. DHA)** associated with ↓ IQ at 8 years (*Am J Clin Nutr.* 2013 Dec;98(6):1575-82)
- **Iodine deficiency** results in ↓ verbal IQ and reading scores at 8-9 yrs (*Evid Based Nurs.* 2013, Dec 12. Epub ahead of print)
- **High homocysteine (↓ B-vitamins)** linked to pregnancy complications and poor cognition in childhood (*Clin Chem Lab Med.* 2005;43(10):1052-7)

Mild iodine deficiency during pregnancy is associated with reduced educational outcomes in the offspring: 9-year follow-up of the gestational iodine cohort.

Hynes KL et al. J Clin Endocrinol Metab. 2013;98(5):1954-62.

- Study: Is **mild iodine deficiency in pregnancy** (UI <150 µg/L) associated **with lower IQ?**
- Results: even mild iodine deficiency during pregnancy can have **long-term adverse impacts on fetal neurocognition**
 - These effects are **not ameliorated by iodine sufficiency during childhood**

Iodine content of prenatal multivitamins in the United States

Leung AM et al. N Engl J Med. 2009;360(9):939-40

“Using the Internet, we identified 127 non-prescription and 96 prescription prenatal multivitamins currently marketed in the United States. Of these multivitamins, 114 (87 non-prescription and 27 prescription) contained iodine”

Iron, Brain Development and Later Neurocognition

- Neonatal **iron deficiency** alters expression of **genes implicated in Alzheimer's disease** (*Brain Research* 2008;1237:75–83)
- Iron is critical for myelination: **↓ dietary levels lead to hypomyelination** (*Glia* 1996;17(2):83–93)
 - Myelin may **increase the brain's resilience to neuropathology later in life**, boosting 'cognitive reserve' (*Expert Review of Neurotherapeutics* 2012;12(6): 629-631)

Maternal vitamin C deficiency during pregnancy persistently impairs hippocampal neurogenesis in offspring of guinea pigs.

Tveden-Nyborg P et al. PLoS One. 2012;7(10):e48488.

- Guinea pigs are appropriate animal models to study vitamin C requirements
 - like humans they cannot synthesize vitamin C but depend on dietary intake
- Study: Marginal prenatal Vit C deficiency led to reduced hippocampal memory function
 - ↓ hippocampal volume ($P < 0.001$); 30% fewer neurons
 - this was not alleviated by postnatal Vit C repletion

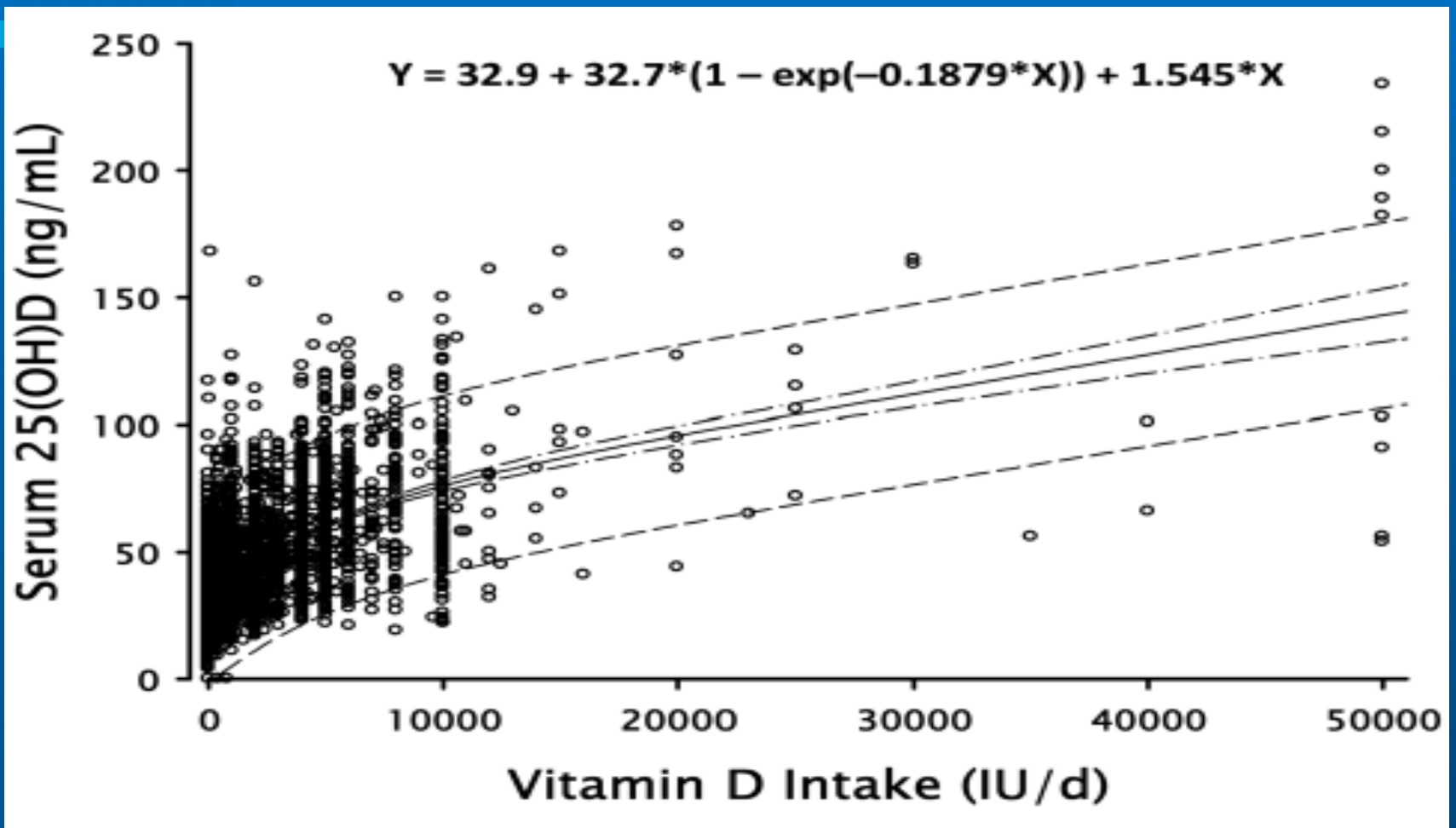
The effects of vitamin D on brain development and adult brain function

Kesby JP^{et al.} Mol Cell Endocrinol 2011;347(1-2):121-7

- Review: vitamin D is **essential for brain development and functioning**
 - Deficiencies in utero and in early childhood linked to **schizophrenia and autism**
- Needed for the **biosynthesis of serotonin, dopamine, nor-adrenaline and adrenaline**
- Deficiencies in adulthood linked to
 - Depression
 - Parkinson's Disease
 - **Alzheimer's disease**
 - **Cognitive decline**

It's blood levels that count...
not how much you take!

Serum 25-hydroxy D intake as a function of vitamin D intake. *Garland CF et al. Anticancer Res 2011;31: 607-11*



Fat and Brain Development



Omega-3 fatty acid deficiencies in neurodevelopment, aggression and autonomic dysregulation: opportunities for intervention

Hibbeln JR et al. Int Rev Psychiatry. 2006;18(2):107-18

- Review: Deficiency of DHA and EPA **in utero** may lower serotonin levels at critical periods of brain development
 - manifests in adulthood as **heightened response to stress**, decreased heart rate variability and ↑BP
- Conclusion: Optimizing **omega-3 EFA intakes during early development and adulthood** may help prevent **later aggression and hostility**

Dietary lipids are differentially associated with hippocampal-dependent relational memory in prepubescent children.

Baym CL et al. Am J Clin Nutr. 2014 Feb 12. [Epub ahead of print]

- Study: Do Western diets influence children's hippocampal-dependent memory?
 - Participants (**n = 52**) aged **7-9 years**
 - Given Food-Frequency Questionnaire and completed memory tasks
- Results: **+ve association between memory and intake of omega 3 fats**
 - Negative association with **saturated fats and sugar**

Choline

- Precursor for acetylcholine (a.k.a the brain's memory manager)
 - In animals, choline supplements in pregnancy result in lifelong memory enhancement
- Precursor for phosphatidylcholine needed for cell membranes
 - Maternal choline deficiency increases the risk of neural tube defects (*Am J Epidemiol* 2004;160:102-9)
- Maternal reserves are depleted during pregnancy and lactation

Choline: needed for normal development of memory.

Zeisel SH. J Am Coll Nutr 2000 Oct; 19(5Suppl):528S-531S

*“The mother's dietary choline **during a critical period in brain development of her infant** influences the rate of birth and death of nerve cells..... These changes are so important that we can pick out the groups of animals whose mothers had extra choline **even when these animals are elderly**.*

*Thus, **memory function in the aged rat** is, in part, **determined by what the mother ate.**”*

Diet and Choline

- Two fatty foods – **eggs and liver** – traditionally provided most of our **dietary choline intake** in Europe and North America
 - In Asian diets choline is **also obtained from soy** – **esp. full fat tofu**
- Recent studies show that **pregnancy greatly increases fetal demands for choline**
 - Current **dietary intake may be too low to meet the demands of the developing fetus** (*Am J Clin Nutr.* 2013 Dec;98(6):1459-67)

*“.....when there isn't enough food, the body has to **make a decision about how to invest the limited foodstuffs available**. Survival comes first. Growth comes second. **In this nutritional triage, the body seems obliged to rank learning last**. Better to be stupid and alive than smart and dead.”*

Carl Sagan. Literacy – The Path to A More Prosperous, Less Dangerous America.
Parade Magazine, March 6, 1994.

Stress, IQ and Pregnancy



Elevated maternal cortisol levels during pregnancy are associated with reduced childhood IQ

LeWinn KZ et al. Int J Epidemiol. 2009;38(6):1700-10.

- Study: Looked for links between maternal cortisol in 3rd trimester and IQ in offspring at age 7
- Results: Maternal cortisol levels were negatively related to full-scale IQ
 - This effects was driven by higher verbal IQ scores
- Within sibling pairs, the highest quintile of cortisol exposure was associated with verbal IQ scores 5.5 points lower

Vitamin C, Cortisol and Stress

- Most animals make vitamin C endogenously
 - Such animals **rapidly increase their vitamin C output under stress** – 5-20 fold depending on species (*Milton K. Comp Biochem Physiol A Mol Integr Physiol* 2003;36(1): 47-59)
- Study: Healthy humans subjected to acute psychological stress **before and after 14 days of vitamin C** (1g sustained-release tid)
 - After vitamin C they had **↓ BP, ↓ salivary cortisol** (*Brody S et al. Psychopharmacology (Berl)*. 2002;159(3):319-24

Recommended Daily Allowances for Vitamin C

Man-L S. Yew. PNAS 1973;70(4) 969-972

- Study: Immature Guinea pigs fed **low, intermediate and high levels of vitamin C**
- Given surgery and then evaluated for
 - recovery time after anesthesia; **wound healing and growth rates**
- They needed **1.5 mg/kg/day to prevent scurvy** (40% more than the RDA for humans)
 - **16 mg/kg/day for optimal growth** (10-fold increase)
 - **50 mg/kg/day for recovery from surgery** (↑ 33-fold)

Rates of vitamin C synthesis in mammals (mg/kg/day)

Species	Low	High (stress)
Goat	33	190
Rat	39	199
Mouse	34	275
Rabbit	9	226
Dog	5	40
RDA for Humans	0.9	No value given

Levine M. New concepts in the biology and biochemistry of ascorbic acid. N Eng J Med 1986:892-902

Magnesium and Pregnancy

Magnesium and Pregnancy

- Fetal demands for Mg during pregnancy generally exceed supply
 - Pregnancy **should be considered a condition of 'physiological hypomagnesemia'** (*Med Sci Monit.* 2001;7(2):332-40)
- Functional markers of magnesium deficiency common in pregnancy include
 - **Nocturnal leg cramps, increased blood pressure, shortness of breath/wheezing, frequency of urination, constipation**
- Severe deficiency **can lead to pre-eclampsia**

Nutrition in Infancy and Childhood



Effects of being born small for gestational age on long-term intellectual performance

Lundgren EM et al. Best Pract Res Clin Endocrinol Metab. 2008;22(3):477-88.

- Review: Being born small for gestational age (SGA) increases risk of lower IQ, behavioural problems, and poor academic performance
 - breast feeding for $\geq 6m$ favourably modifies these effects
- Nutrient-enriched formulas have no advantages when it comes to intellectual development
 - Increases risk of rapid weight gain and eventual obesity

Durham Dyspraxia Trial

Durham Educational Authority, Durham, UK

- Dyspraxia: Difficulty drawing, writing, buttoning clothes or other tasks needing fine motor skills
 - Often co-exists with ADHD and dyslexia
- 100 children at 12 schools in Durham county given either fish oil or placebo capsules (RCT)
 - Over 1 yr 12,000 assessments were undertaken
- Trial looked at Dyspraxia and Motor skills, but there were also full assessments for Dyslexia and ADHD

*“The response has been very encouraging. In very broad terms, we saw that **up to 40 per cent of children on the trial showed dramatic improvements.***

*In some individual cases, we saw reading age gains of between 18 months and four years, **and attention gains of as much as 400 percent.**”*

Dr Madeleine Portwood, Senior Educational Psychologist, Durham County

ADHD Now, Dementia Later?

- Hypothesis: Many neurochemical anomalies seen in **ADHD overlap with alterations seen in late-life dementias** (*Curr Psychiatry Rep.* 2012 Oct;14(5):552-60)
 - Includes **Alzheimer's, dementia with Lewy bodies, and frontotemporal dementia**
- Cohort Study Findings: Adults with a **history of ADHD have x3 times the risk of developing Lewy body dementia** later in life (*Eur J Neurol.* 2011;18(1):78-84)
 - **No link seen to Alzheimer's** or mild cognitive impairment

Prenatal Supplements

– suggested protocol –

Supplemental nutrients before and during pregnancy (1)

- Multivitamin: higher B-vitamin content (all B vitamins, not just folic acid)
 - Preferable to have folic acid in coenzyme form
 - Additional B12 (sublingual methylcobalamin)
- Time-released vitamin C – 1g bid
 - Increase by 1g/day per trimester
- Fish oil or algal supplement for vegetarians

Supplemental nutrients before and during pregnancy (2)

- Additional choline: Especially if not eating eggs
 - Given as phosphatidylcholine
 - 2-3 gel caps = 1-2 egg yolks
- Vitamin D: Check 25-hydroxy D if possible
 - minimum 2000 IU/day; 4000 IU safe in pregnancy and prevents preterm labour and infections (*J Steroid Biochem Mol Biol. 2013;136:313-20*)
- Magnesium: 100mg magnesium glycinate bid. Preferably, increase gradually to bowel tolerance

“The evidence is clear that inadequate magnesium intake is common during pregnancy and that the plasma levels of magnesium tend to fall, especially during the first and third trimesters of pregnancy.”

Dr. Mildred S. Seelig MD

Diet in pregnancy

- High fruit and vegetable
 - Minimum 8 servings; aim for 10-12
- Low glycemic load
 - Low or no sugar
 - All starches should be wholegrain
- Good fats at each meal
 - Fatty fish, nuts, seeds, olive oil
 - 1 – 3 eggs a day (organic, free-range or omega 3)
- 4-6 oz protein with each meal

The Ageing Brain and Nutrition

Dementia and Nutritional Deficiencies

- Protective effects seen with higher plasma levels of **B1, B2, B6, folate, B12, C, D, E, and omega-3 fatty acids** (Bowman GL et al. *Neurology* 2012;78(4):241-9)
- **Adequate 25-hydroxy D levels** (Buell JS et al. *J Gerontol A Biol Sci Med Sci.* 2009;64(8):888-95)
- Minerals: Especially **iron, zinc and magnesium** (Ames BN et al. *Mol Aspects Med.* 2005;26(4-5):363-78)

SCIENTISTS SAY
THAT STRESS CAN
SHRINK THE BRAIN.

HEY,
THANKS
A LOT.

THAT'LL
HELP ME
RELAX!



*LaMontagne
Cartoonist*

More than the sum of its parts? Nutrition in Alzheimer's disease.

von Arnim CA et al. Nutrition. 2010 Jul-Aug;26(7-8):694-700

- Review: discusses importance of **malnutrition and micronutrient deficiencies in Alzheimer's disease** and recent supplementation trials
 - Evidence that **malnutrition, oxidative stress, and deficits of homocysteine-related vitamins** are involved in pathogenesis
- Available **data do not support supplementation of individual micronutrients** for prevention/treatment
 - However, approaches with **multiple nutritional components** might be promising

Case study

- Frontal Lobe Dementia -

Frontal Lobe Dementia

- The patient: Female; Caucasian, 68 yrs.
Retired teacher
 - Non-smoker , non drinker
- Life-long **history of depression**
- Married
 - Had had **two children born with spina bifida; one survived**
 - One **physically normal child with chronic depression**

Diet and Lifestyle

- Exercise: Played tennis daily for prolonged periods
 - “*Only way to reduce stress*”
- Diet: Little interest in food but stayed away from junk. Often skipped meals
- Supplements: Started comprehensive regime of supplements in May 1999
 - Benefited at first, but compliance was poor
 - Lost to follow-up in 2002

Frontal Lobe Dementia

- Returned to clinic in 2009. Seeing neurologist because of memory and speech problems
- Speech: slow, hesitant. Stuttered sometimes
 - Couldn't "get the right word out." Often used wrong or unrelated words, mispronounced words
 - Had to simplify speech. Used only "little words"
- Behavioural changes: apathy, restlessness, irritability, aggression, felt suicidal
- Still playing tennis, but couldn't focus
 - Accuracy went; no energy. Couldn't play bridge, because she couldn't remember the cards

Frontal Lobe Dementia

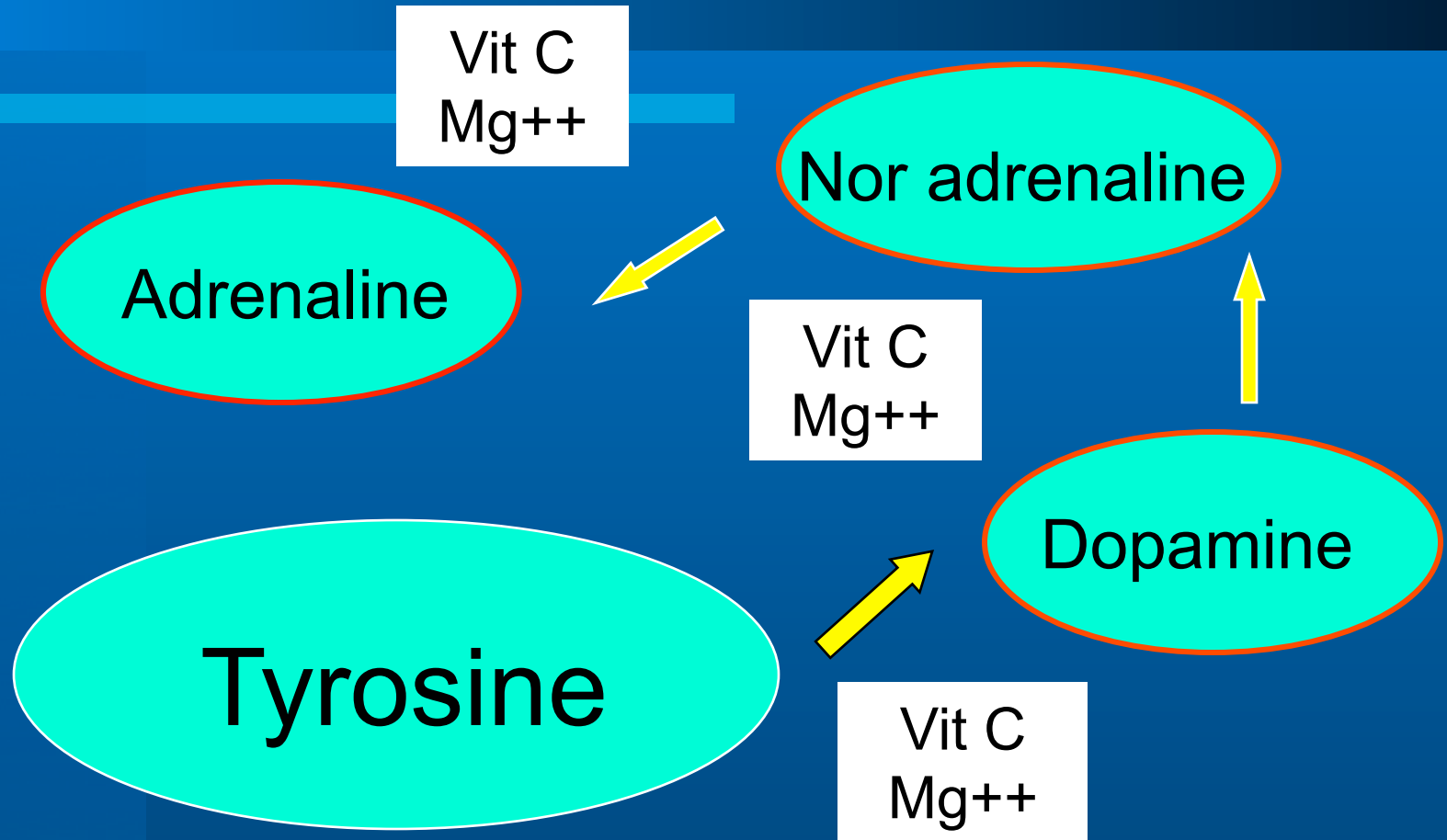
- Diagnosis: Frontal lobe dementia
 - CT scan showed generalized cerebral atrophy
 - SPECT scan showed severe frontal lobe hypoperfusion
- Supplements: Still occasionally taking them but not original recommendations
 - No fish oil, little magnesium, 2000 IU vitamin D
 - B12 tested: 178pmol/L on 1mg/day sublingual methylcobalamin

Frontal Lobe Dementia

- Plan: Back on supplements as originally recommended (**similar to pregnancy regime**)
 - Additional B-vitamins (in co-enzyme form)
 - 5mg B12 (methylcobalamin)
- Diet: Increase vegetables and fruit (8-10 servings a day)
 - Include **high quality protein with every meal; low starch, no sugar**
- Additional **supplements to support memory, speech and word recall**

Stress, Speech and Dopamine

- Dopamine is **involved in speech**
 - Needed for verbal fluency and word recall
- The precursor for dopamine is the non-essential amino acid tyrosine
 - under **stressful conditions tyrosine becomes essential**
- Dopamine is, in turn, the precursor for nor-adrenaline
 - Nor-adrenaline **is further metabolized to adrenaline**



Additional Supplements

- Tyrosine: Required for dopamine synthesis
- Citicoline: Precursor for acetylcholine required for memory; neuroprotective; enhances brain dopamine (*Ann N Y Acad Sci. 2000;920:332–335*)
- L-theanine: an amino acid unique to tea.
 - Animals suggest improvement in learning and memory (*J Herb Pharmacother. 2006;6(2):21-30*)
 - Calming: increases serotonin, dopamine, GABA

Additional Supplements

- Tyrosine: 4x 600mg on waking, empty stomach, wait 30 mins before eating
 - 2-3 extra mid-late afternoon (if needed) **and before any stressful event**
- Citicoline: 500mg bid
- L-theanine: 250mg in the morning and before bed
 - Instructed to **take an extra capsule as needed during the day for anxiety**

Outcome

- Patient began to improve (no medications)
 - One year after starting supplements, was told she was “high functioning”
- By early 2013 memory and speech normal
- May 2013: tested at Baycrest clinic

“My results are better than they were 2 ½ years ago and now [the doctor] says I do not have frontal lobe dementia. She feels my speech problems were the result of years of severe stress”

Conclusions

- Nutrition in utero **effects cognitive development**
 - In turn, higher **childhood IQ** may protect against **cognitive decline in old age**
- To be effective, **dementia prevention programs must focus on nutrition throughout the lifespan**
- Not all forms of dementia reflect irreversible degenerative disease
 - Standard **orthomolecular approaches** may be **effective** in reversing some early dementias