Vitamin D and mental disorders – cause, consequence or coincidence?

John McGrath
Is it a vitamin or a hormone?

• When sufficient exposure to sunshine, no need for dietary input, thus it is not a ‘vitamin’.
• Seco-steroid – shared metabolic and signalling pathways with other steroid hormones.
• Endocrine pathways tightly regulated by calcium and parathyroid hormone
• Provides broad signalling information at distal organs.
Autocrine and paracrine pathways

- Broad range of roles in immune function, cardiovascular health, brain development.
- Involved in *cell cycle regulation*
• Dietary sources
  • Fatty fish
  • Fortified food (some milk, margarine, etc)
  • Supplements
Vitamin D production is linked to:

• season
• latitude
• skin colour
• BMI
• clothing cover

•** behaviour **
The vitamin D hypothesis

Low pre- and perinatal vitamin D impacts adversely on brain development, leaving the affected offspring at increased risk of schizophrenia.

(Think folate and spina bifida)

The vitamin D receptor (VDR) and 1α hydroxylase are present in the human brain.


The vitamin D receptor is present in every DA neuron in the Human Substantia Nigra

Cui et al. Neuroscience 236 (2013) 77–87
Developmental vitamin D (DVD) model

Mothers
- Normal diet
- Vitamin D deficient diet

Pups
- Control pup
- Deficient pup

Adults
- 10 week adult
Does low prenatal vitamin D alter brain development?

- Yes – *in the rat!!*
Q: Do people with schizophrenia have low vitamin D?
A: Yes – but so too do many people with other chronic disorders.
Background

Sources of variance

Sun exposure
Diet
Season
Vitamin D
Supplements
Latitude
Genetic factors

Primary aims:

• GWAS of 25 hydroxyvitamin D (25OHD) to identify quantitative trait loci (QTL)

• Mendelian randomization to identify putative causal relationships

Vitamin D team

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Main GWAS findings in EUR
- 143 loci associated with 25OHD levels, implicating genes in relevant pathways:

**Functional annotation**
- FUMA | LDSC | SMR

**Skin properties**
- HAL, KLK10, FLG, FLG-AS1, POU2F3, PADI1, DSG1

**Lipid and lipoprotein pathways**
- PCSK9, DOK7, CELSR2, LIPC, GALNT2, ABCA1, DGAT2, CETP, APOE, APOC1, \( \text{APR} \), \( \text{AKR1A} \), \( \text{APOB} \), \( \text{CETP} \), \( \text{LIPG} \), \( \text{LDLR} \)

**CYP450 and steroid-related enzymes**
- HSD17B1, CYP2R1, \( \text{CYP7A1} \), \( \text{CYP26A1} \), \( \text{HSD3B1} \), \( \text{CYP24A1} \)
Bidirectional Mendelian randomization -

• Do the genes associated with 25 hydroxyvitamin D concentration predict risk of mental disorders?
  • NO (but are linked to dyslipidemia)

• Do the genes associated with mental disorders predict 25 hydroxyvitamin D concentration?
  • YES !!
    • Schizophrenia
    • Major depression
    • Bipolar disorder
    • Educational achievement
NO
Vitamin D and brain health

Rodents - low vitamin D disrupts brain development and adult brain function

Low neonatal vitamin D is associated with an increased risk of schizophrenia, ADHD, ASD

Does low adult vitamin D exacerbate brain disease – two hit hypothesis?
VISIBILITY

Peak of Inflated Expectations
Plateau of Productivity
Slope of Enlightenment
Trough of Disillusionment
Technology Trigger

TIME

KEEP CALM AND DEMAND EVIDENCE
acknowledgements