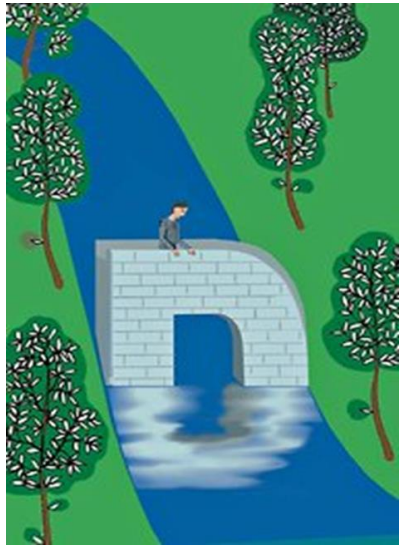
NIELS BOHR PROFESSORSHIP

PSYCHIATRIC EPIDEMIOLOGY



Virtual International Congress 2021

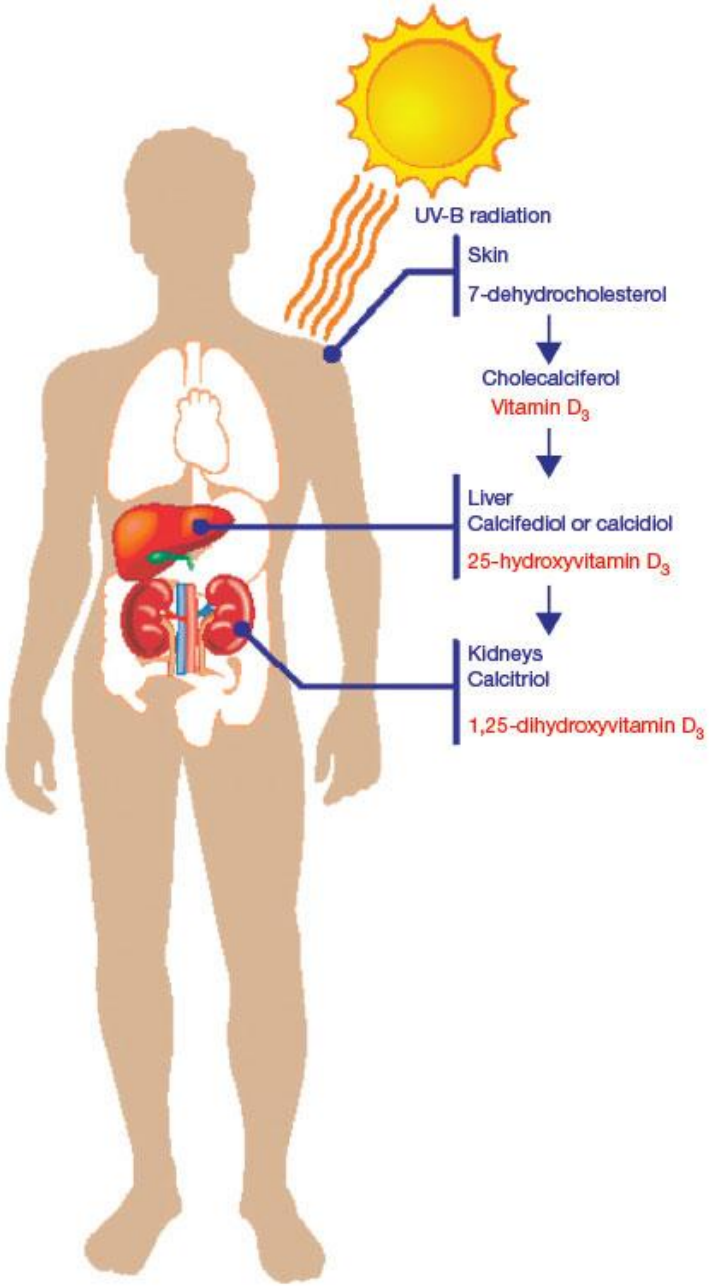
21 - 24 June, 2021

RC PSYCH

ROYAL COLLEGE OF PSYCHIATRISTS

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

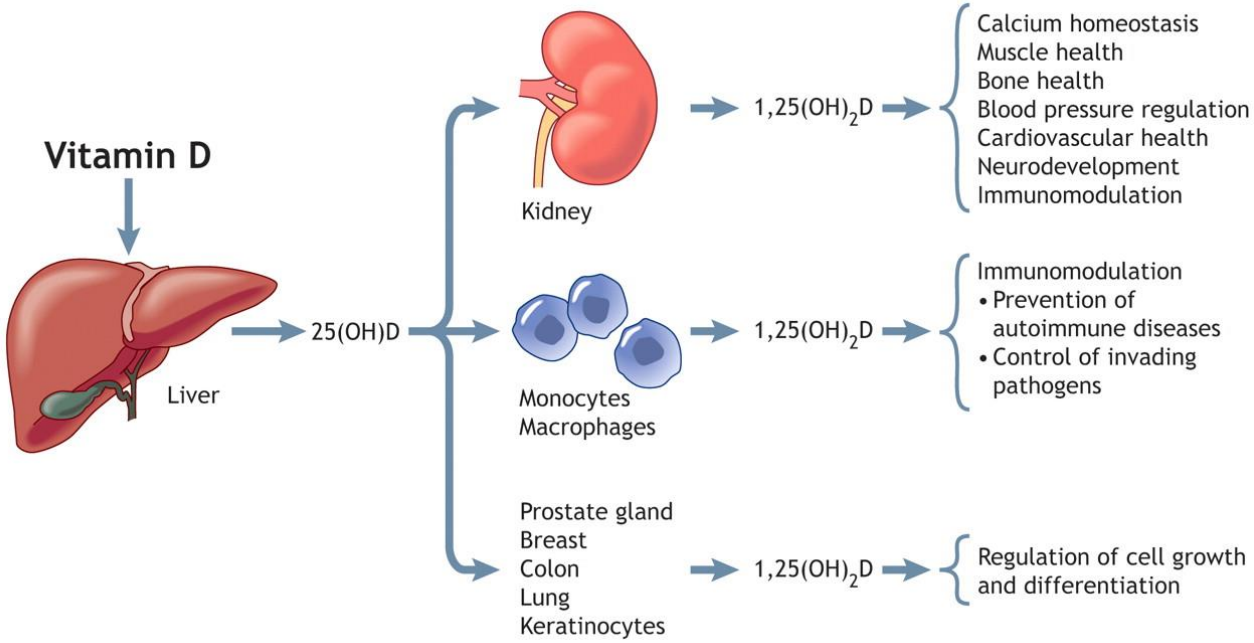
John McGrath



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 ***

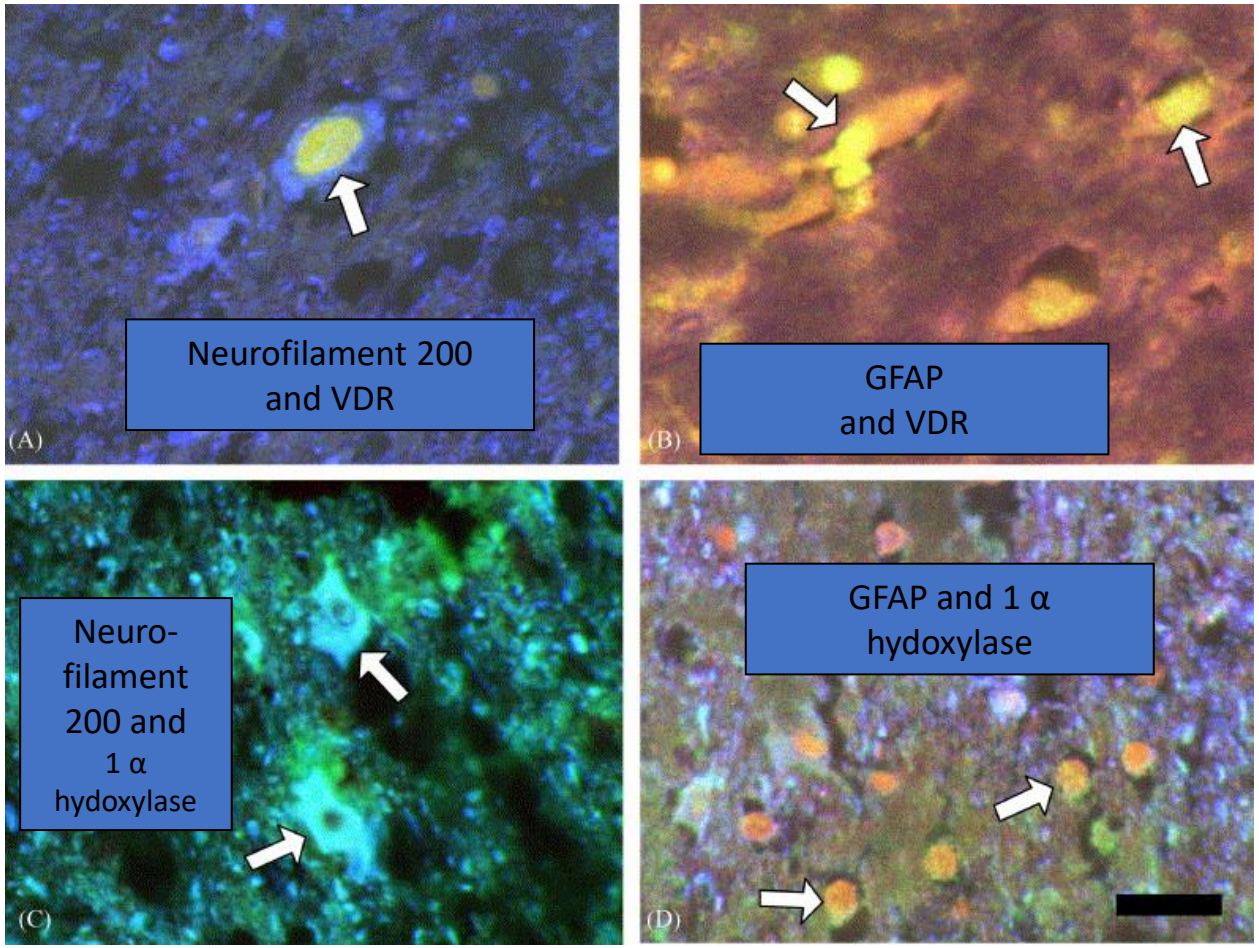
The vitamin D hypothesis

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)

McGrath J. (1999) Hypothesis: Is low prenatal vitamin D a risk-modifying factor for schizophrenia? *Schizophrenia Research* 40: 173-177.

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

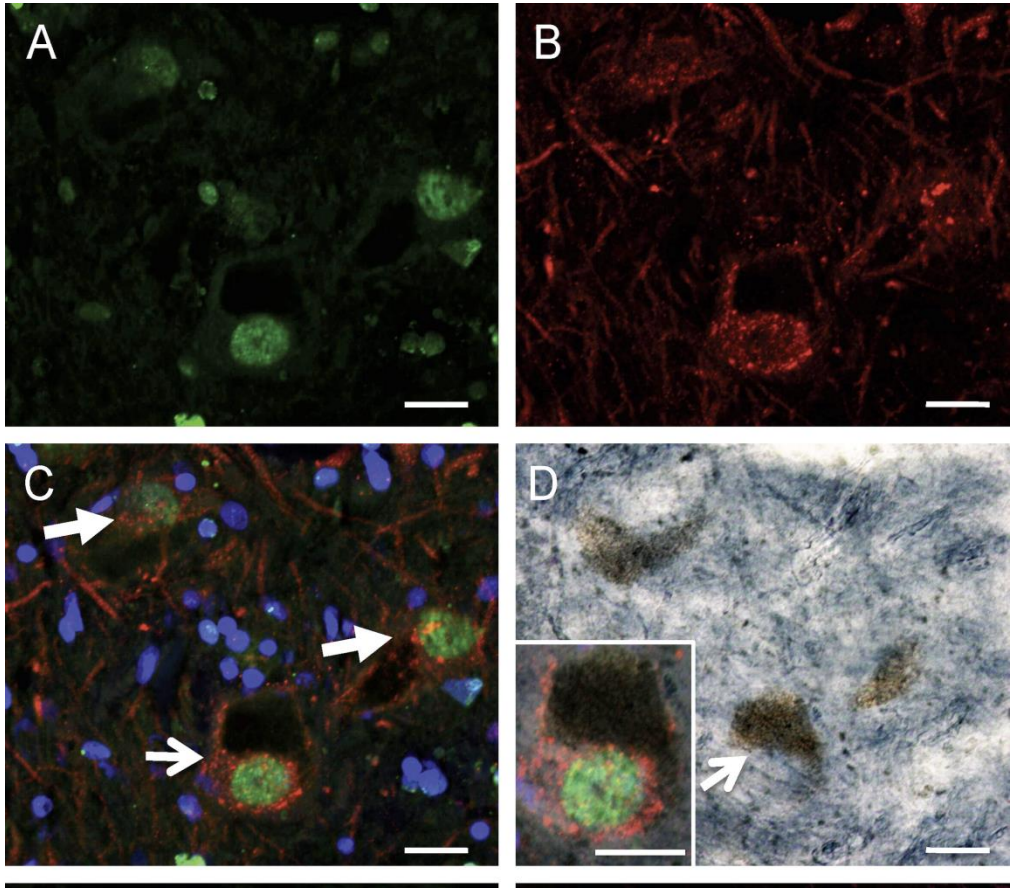


McGrath et al. Vitamin D: the neglected neurosteroid? **Trends in Neuroscience.** 2001;24(10):570-2.

Eyles et al (2005) Distribution of the vitamin D receptor and 1-hydroxylase in human brain. **J Chem Neuroanat**: 29(1):21-30.

Cui et al (2013) The vitamin D receptor in dopamine neurons; its presence in human substantia nigra and its ontogenesis in rat midbrain. **Neuroscience**. 236:77-87.

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

10 week adult

Does low prenatal vitamin D alter brain development?

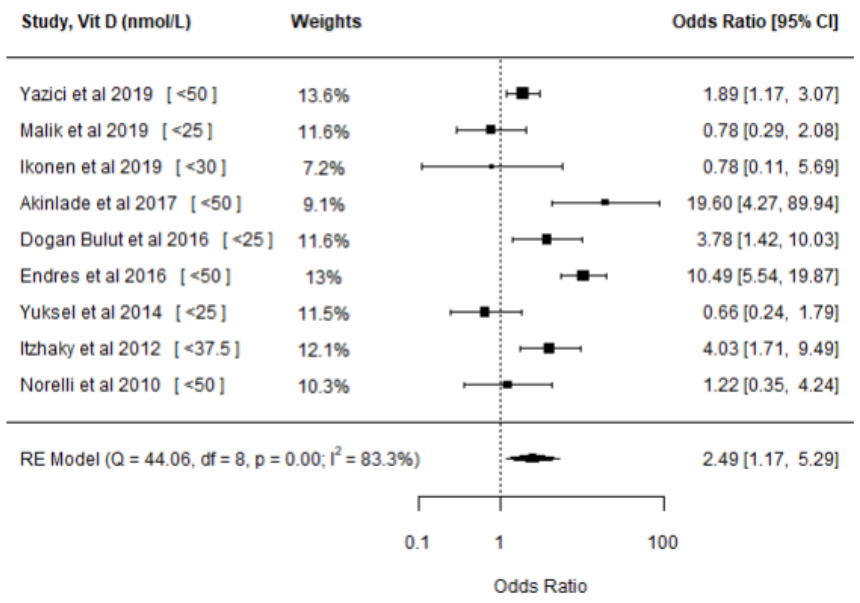
- *Yes – in the rat!!*

Q: Do people with schizophrenia have low vitamin D?

A: Yes – but so too do many people with other chronic disorders

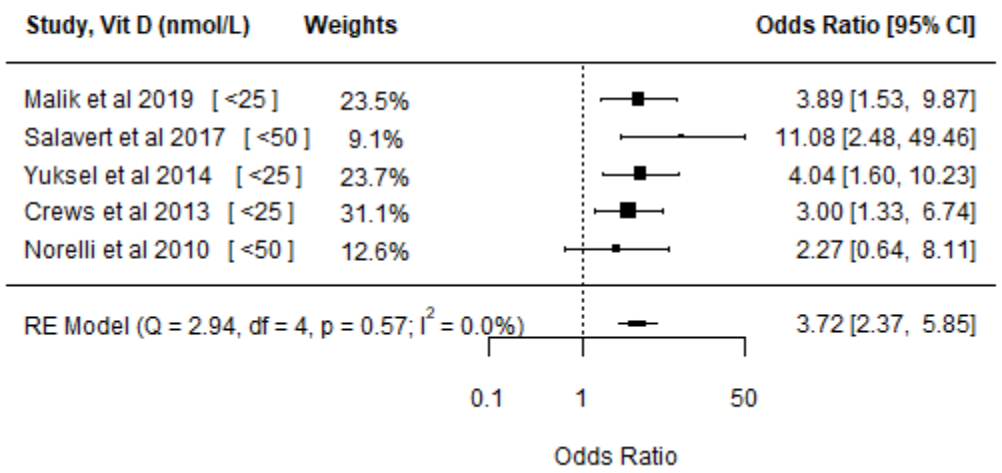
Supplementary Figure 3. Forest plot of the Odds Ratio of vitamin D deficiency in schizophrenia patients vs. healthy controls

A

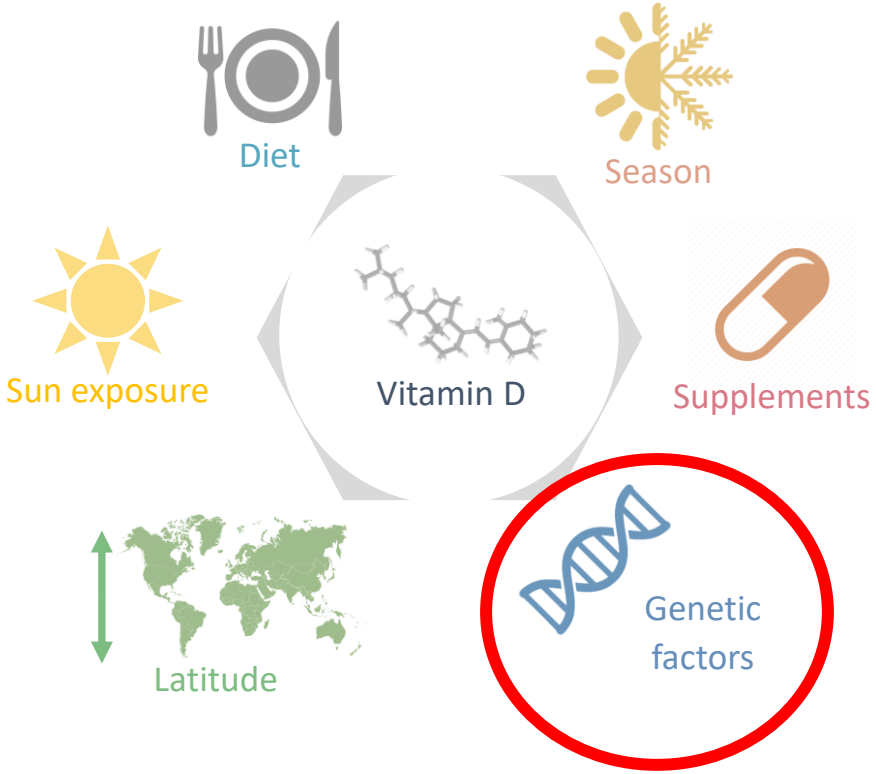


B

Supplementary Figure 5. Forest plot of the Odds Ratio of vitamin D deficiency in FEP vs. healthy controls.



Sources of variance



Vitamin D team

Prof Naomi Wray

Dr Joana Revez

Prof John McGrath

biobank uk

Primary aims:

- GWAS of 25 hydroxyvitamin D (25OHD) to identify quantitative trait loci (QTL)
- Mendelian randomization to identify putative causal relationships

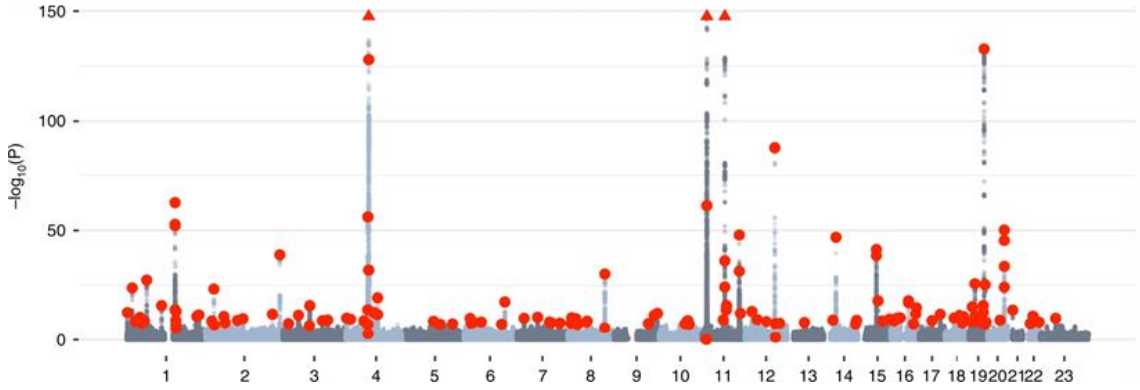
nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-020-15421-7 OPEN

Genome-wide association study identifies 143 loci associated with 25 hydroxyvitamin D concentration

Joana A. Revez[1], Tian Lin[1], Zhen Qiao[1], Angli Xue[1], Yan Holtz[2], Zhihong Zhu[1], Jian Zeng[1], Huanwei Wang[1], Julia Sidorenko[1], Kathryn E. Kemper[1], Anna A. E. Vinkhuyzen[1], Julanne Frater[2], Darryl Eyles[2,3], Thomas H. J. Burne[2,3], Brittany Mitchell[4,5], Nicholas G. Martin[4], Gu Zhu[4], Peter M. Visscher[1], Jian Yang[1,6], Naomi R. Wray[1,2,8] & John J. McGrath[2,3,7,8]



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, DOCK7, CELSR2, LIPC, GALNT2, ABCA1, DGAT2, CETP, APOE APOC1, PLAG2G3, (AKR1A), (APOB), (CETP), (LIPG), (LDLR)

CYP450 and steroid-related enzymes

HSD17B1, CYP2R1, (CYP7A1), (CYP26A1), (HSD3B1), (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

YES

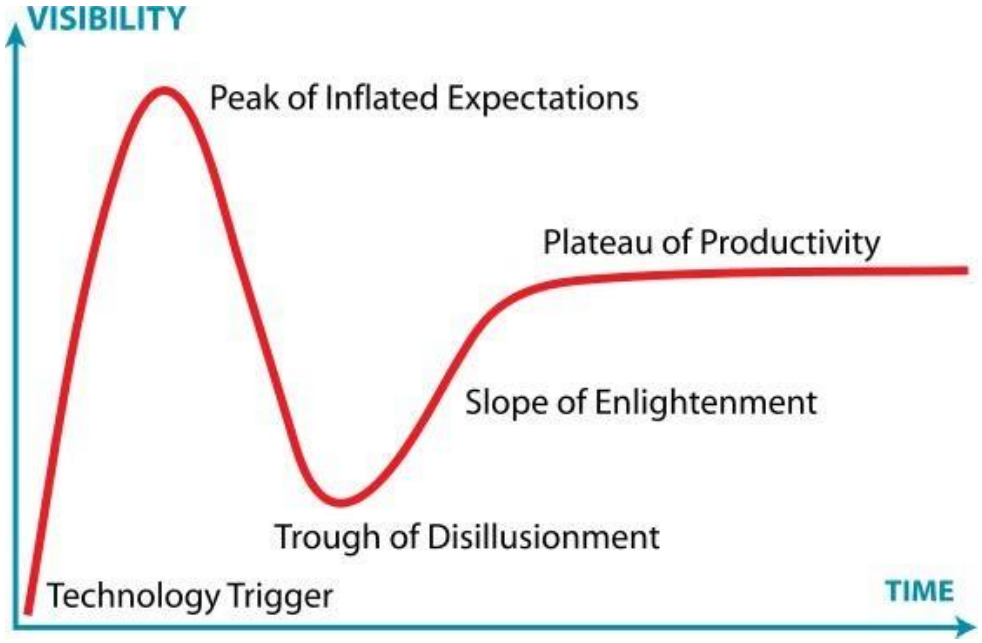
Vitamin D and brain health

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?


NOW!
The Wonder Vitamin D


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


KEEP
CALM
AND
DEMAND
EVIDENCE

acknowledgements

NIELS BOHR PROFESSORSHIP
PSYCHIATRIC EPIDEMIOLOGY

AARHUS UNIVERSITY

Queensland Centre for Mental Health Research

qbi queensland brain institute

THE UNIVERSITY OF QUEENSLAND AUSTRALIA

Danmarks Grundforskningsfond
Danish National Research Foundation