Vitamin D and mental health: reflection on U-shaped relationships

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Schizophrenia

*a neurodevelopmental disorder*

- Neuropathology
- Antecedents
- Early life risk factors
- Genetic factors impacting on brain development
The vitamin D hypothesis

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

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


Vitamin D supplementation study

• Collaboration – Oulu University, Cambridge University
• North Finnish 1966 Birth cohort,
  – n = 9144
  – Vitamin D supplementation during first year.
  – Schizophrenia by age 31
• Association between lack of vitamin D supplementation and increased risk of schizophrenia in males only

Developmental vitamin D (DVD) model

Mothers
- Normal diet
  - Control pup
  - 10 week adult
- Vitamin D deficient diet
  - Deficient pup
  - 10 week adult

Pups

Adults
Compared to control rats, depleted rats have larger ventricle/brain ratio as pups.

DVD behavioural phenotype

Mostly normal, except
- hyperlocomotion
- response to MK801
- response to amphetamine
- response to haloperidol
- altered latent inhibition

- Becker et al (2005) Transient prenatal vitamin D deficiency is associated with subtle alterations in learning and memory functions in adult rats *Behavioural Brain Research* 161
Analytic epidemiology

Measuring 25 OH vitamin D$_3$ in neonatal dried blood spots.

Nested case-control study
Vitamin D assay based on archived dried blood spots


Danish Neonatal Dried Blood Spots
Case-control study

- Record linkage – Biobank and Mental Health Register
- 430 cases of schizophrenia and 430 matched controls.
- Population-based sample

Relative risk (and 95%CI) of schizophrenia for quintiles of 25 hydroxy-vitamin D$_3$

- Lowest  2.1 (1.3 – 3.5)
- Second  2.0 (1.3 – 3.2)
- Third   2.1 (1.3 – 3.4)
- Fourth  reference
- Highest 1.7 (1.04 – 2.8)
Non-linear exposure risk relationship

- Deciles
- Fitted curve
- Reversed J-shaped curve
- Mechanism?
- Population attributable fraction = 44%
Mother-to-child transmission of HIV, and child mortality and their association with maternal vitamin D

Inflection

(54-64 ng/ml)

135-160 nmo/L
Maternal vitamin D versus neonatal small-for-gestational age.

Inflection Aprox 60 nmol/L
Maternal vitamin D status versus type 1 diabetes in the offspring.

Inflection

Aprox 120 nmol/L
Serum 25-hydroxyvitamin D versus IgE

Inflection

Aprox 120 nmo/L
Vitamin D status and risk of mortality.

Inflection

Aprox. (40 ng/ml)
100 nmol/L
Vitamin D status and mortality in older men

Inflection

Aprox 80 nmol/L
Baseline 25OHD versus all cause mortality
N = 247,574
The gloomy prospect of U-shaped relationships

Why do we keep seeing non-linear exposure-risk relationships?
What is the meaning of a U- or J-shaped relationship?

• Is it ‘true’ – like *in vitro* steroid response?
• Is it a population wide effect?
• Is it an admixture of underlying subgroups that could be stratified by some variable?
Admixture – how to stratify the population

• Group-specific component (binding protein) may impact on free fraction
  – Different affinity?
  – Different serum concentrations?
**Ancestral type**

Affinity = *high*

Binding protein concentration = normal

Total 25OH molecules = 5
Free 25OHD molecules = 2
Ancestral type

Affinity = high

Binding protein concentration = normal

Total 25OH molecules = 5
Free 25OHD molecules = 2

Derived type

Affinity = lower

Binding protein concentration = lower

Total 25OH molecules = 5
Free 25OHD molecules = 4
Admixture – how to stratify the population

- ‘Mild vitamin D resistance’
  - CYP27B1 variants?
  - organ specific resistance?
Admixture – how to stratify the population

- Could high calcium intake throttle-back PTH and 1,25OHD dynamics?
- Related species?
  - C3 epimer
  - sulphated vitamin D
- Gaps in the knowledge base:
  - Transporters for bound and unbound ligands?
Do we still love vitamin D?
Future directions

• There is an urgent need to explore the mechanisms underlying the U-shaped curve.
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