# Vitamin D, Mood and the Mind

Experiences of the Tuda Study

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# Acknowledgement


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- Watts Fellow
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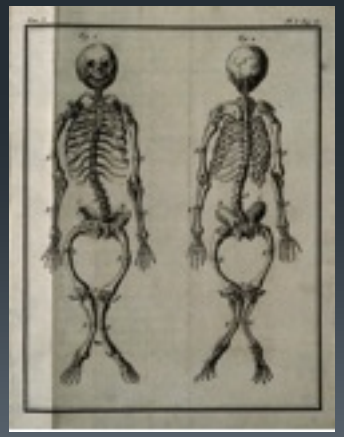
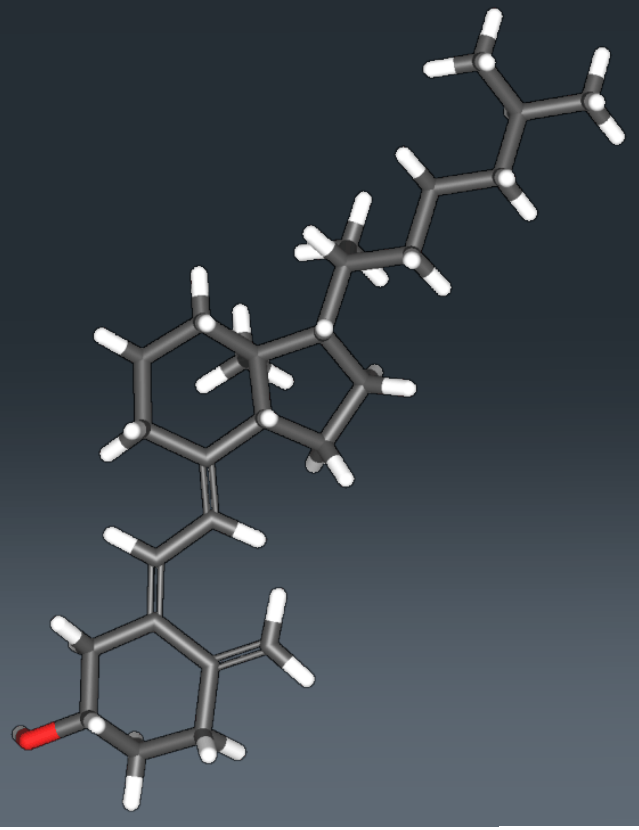
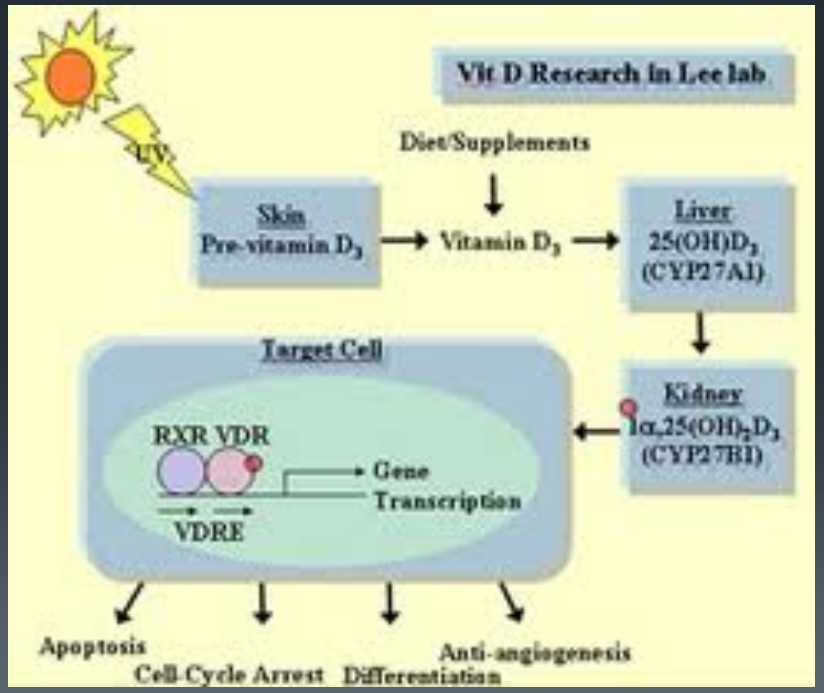


# Vitamin D

- A fat soluble steroid produced by action of sunlight on skin -1920s
- Dietary intake from oily fish, fortified foods or supplements



# Vitamin D Receptor -1969




- Nuclear receptor found in many cells in the body
  - Bone
  - Muscle
  - Cancer cells
  - Central Nervous system
- Increases intestinal absorption of calcium
  - Numerous direct cellular effects – influences over 200 genes identified to date

# Clinical effects of vitamin D

- Bone
  - Increases Bone Mineral Density
  - Reduces fractures
- Muscle
  - Increases muscle strength
- Cardiovascular disease
  - ?
- Cancer
  - ?
- Brain
  - ?

# Vitamin D deficiency

- <25nmol/l Severe deficiency
- 25-50nmol/l Deficiency
- 50-75 nmol/l “Insufficiency” (US Endo Soc) vs replete (US IOM)
- >75 nmol/l Replete

- 1 billion people Vitamin D deficient or insufficient
- US 50% Vit D deficient and 75% insufficient

# Vitamin Deficiency in Ireland

| Prevalence of Vitamin D deficiency (< 50 nmol/l) in Ireland | | | | |
|---|---|---|---|---|
| **Author** | **Size** | **Population** | **Prevalence (%)** | **Other Comments** |
| Cashman et al., 2013 | 1132 | Adults aged ≥ 18 years | 40.1 | Year round figure |
| Hill et al., 2008 | 1015 | 12-15 years old in Northern Ireland | 36.0 | Adolescent group |
| Lardner et al., 2011 | 143 | Community dwelling middle aged females | 47.0 | Not on supplements |
| Hill et al.,2006 | 95 | Healthy postmenopausal females (51-75 years) | 48.0 | In Winter, not on supplements |

# Vitamin D and the Brain

- Vitamin D metabolites discovered in CSF of healthy adults (1984)
- Vitamin D receptor widely expressed in the brain
  - temporal, orbital and cingulated cortices, cerebellum, mesopontine area, thamalus, hypothalamus, in the accumbens nuclei, parts of the stria terminalis and amygdala and widely throughout the olfactory system (McCann et al., 2008)
- Multiple gene targets in the brain

# Vitamin D Gene Products in the Brain

| $1,25(OH)_2D$ Gene Target Products in the Brain | | |
|---|---|---|
| | **Effect** | **Role** |
| **Neurotrophins** | | |
| Nerve Growth Factor (NGF) | Up regulates | Important for growth and survival of many cells including cholinergic basal forebrain neurons. |
| Neurotrophin –3 (NT-3) | Up regulates | Increases transmission in hippocampal cells, also found in neocortex. |
| Glial Derived Nerve Growth Factor (GDNF) | Up regulates | Reduces oxidative stress in Parkinson's Disease. |
| **Calcium Binding Proteins** | | |
| Calmodulin, Parvalbumin, Calretinin | Up regulates | Calcium signalling and homeostasis. |
| **Enzymes** | | |
| Gama Glutamyl Transpeptidase | Up regulates | Enhances innate antioxidant pathways by increasing production of glutathione – protects integrity of nerve conduction pathways. |
| Nitric Oxide Synthetase | Down regulates | GENERATES NITRIC OXIDE WHICH CAN CAUSE DAMAGE TO NEURONS AT HIGH CONCENTRATIONS |
| Choline AcetyLtransferase | Up regulates | Responsible for neurotransmitter acetlycholine known to play a role in memory function. |
| **Cell Signalling Proteins** | | |
| N-myc, c-myc, protein kinase C | Up regulates | **CONTROL OF CELL CYCLE, DIFFERENTIATION AND PROLIFERATION.** |
| **L-Type Voltage Sensitive Channels** | Up regulates | REGULATION OF NEURONAL CALCIUM -ROLE IN NEUROTRANSMISSION, NEUROGENESIS,, HIPPOCAMPAL CELL LOSS. |
| **Cytokines (l1-b, Il- 2)** | Down regulates | Mediates inflammation and neuronal damage. |

# Animal studies

- VDR Knockout Mice
  - Premature ageing, anxiety
- Vitamin D deficiency Mice
  - Normal working memory but disrupted attention
- Vitamin D supplementation of aged rats was found to increase β-amyloid clearance and decrease amyloid burden (Briones et al., 2012).
- It also ameliorated the age related decline in learning and memory. In addition, a vitamin D enriched diet was correlated to a decrease in amyloid plaques and Aβ amyloid peptides in transgenic mice (Yu et al., 2011).

# Cross sectional studies - Cognition

**Cross Sectional Studies of 25(OH)D and Cognition**

| Author | No. | Age | Test/ Measure | Association | Comment |
|---|---|---|---|---|---|
| McGrathet al.,2007 | 9556 | 20-59<br>60-90 | Adult group: DDST,SDLT<br>Elderly: Short storyrecall | No | Brieftestinelderly |
| Slininet al.,2012 | 5257 | 76.6 | ModifiedMMSE(3MS),TMB | Yes | Botht ests when25(OH)D <25nmol/lversus ≥ 75nmol/l |
| Tolpannenet al.,2011 | 4310<br>4290 | 60-90<br>20-59 | Olderadults:storyrecall<br>Youngeradults: DSST,SDLT | No | |
| Llewellyne t al.,2010 | 3325 | 73.7 | WAIS digitspan,limitedMMSE, EBMT(story recall),GCS,MCS | Yes | Onlyattention,oriet antionwhen25(OH)D 25 –50nmol/l,no confounds |
| Leeet al.,2009 | 3133 | 60.0 | DSST,ROCT,CTRM, | Yes | OnlywithDSST |
| Llewellyne t al.,2009 | 1766 | 78.2 | AMT | Yes | Onlyinmalesinfullmodel,someubjectinstitutionalised |
| Buellet al.,2009 | 1080 | 75.0 | TrailsA&B,DSST,WMSlogicalmemoryand subtests | Yes | Executive testsonlyandwhen25(OH)D <25nmol/l |
| Chanet al.,2011 | 939 | >65 | CSI-D | No | Inmaleswhencomparing25(OH)D <63nmol/lvs.>92 nmol/l |
| Anweillere t al.2010 | 762 | 80.7 | SPMSQ | Yes | Below 25nmol/lincreasedrisk |

**Cross Sectional Studies of 25(OH)D and Cognition**

| Author | No. | Age | Test/ Measure | Association | Comment |
|---|---|---|---|---|---|
| MeNantet al.,2012 | 463 | 78.0 | MMSE,DSMTTMTA&B,TMTdiff,BlockDesignScore | Yes | Below 50mol/lreducedscore inTMTB& BDS |
| Seamanset al.,2010 | 188 | 76.2 | CANTAB | Yes | Onlyinfemales |
| Oudshoornet al.,2008 | 225 | 77.7 | MMSE | Yes | |
| Petersonet al.,2012 | 159 | 85 | CDR,MMSE | No | Noadjustmentforseason |
| Jordet al.,2006 | 148 | 62.1 | TrailsA&B,memory,language&executive tests | No | Mayhavebeenunderpowered |
| Skalkset al.,2012 | 138 | 79.6 | AMT | Yes | Higherriskwhen25(OH)Dbetween(23.26 - 47.8nmol/l,noconfounds |
| Lasaiteet al.,2011 | 130 | 18-26 | DST,TMA&B | No | Noadjustmentforconfounds |
| Brouwer-Bolsmaet al.,2013 | 127 | 65+ | Executivefunction | Yes | |
| Anweillere t al.2010 | 95 | 71.1 | MildCognitiveImpairment(Winbladeet al.criteria) | Yes | |
| Wilkinset al.,2006 | 80 | 74.8 | CDR,SBT,MMSE,Language,Memory,Executive tests | Yes | OnlywithSBT&CDR,Somesubjectswith dementia |
| Aungeet al.,2007 | 44 | ≥ 65 | MMSE,CDT | No | Noadjustmentforconfounds |
| Przyelskiet al.,2007 | 32 | 79.5 | MMSE | Yes | Noadjustmentforconfounds |
| Hansenet al.,2011 | 25 | 34.6 | N-Backtest,accuracy&reactiontime | Yes | Noadjustmentforconfounds |

DSST - DigitSymbol Substitution Test,DSMT- DigitSymbol Matching Test,AMT - Abbreviated Mental Test,CDR– Clinical Dementia RatingScale,CANTAB – Cambridge Neuropsychological Testing Automated Battery,MMSE – Mini Mental State Examination, SBT – Short Blessed Test, TMA&B –Trail making A & B. [Ages quoted as range or mean]

15 of 22 cross sectional studies showed positive associations between vitamin D levels and cognition

# Cohort Studies - Cognition

| Longitudinal Studies of 25(OH)D and Cognition | | | | | | |
|---|---|---|---|---|---|---|
| **Author** | **No.** | **Age** | **Length (yrs)** | **Cognitive Outcome** | **Inverse Association** | **Comment** |
| Slinin et al. , 2012 | 6257 | 75.0 | 4 | Modified MMSE , Trails B | Yes | Only with modified MMSE when 25(OH)D <25 or 25-49.9 nmol/l versus ≥ 75 nmol/l) |
| Breitlin et al., 2012 | 1639 | ≥ 65 | 5 | COGTEL | Yes | Yes |
| Slinin et al., 2010 | 1604 | 74.6 | 4.6 | Modified MMSE, Trails B | No | No |
| Lewellyn et al., 2011 | 858 | >75 | 3-6 | MMSE, Trails A & B | Yes | Both tests, significant when comparing (<25 versus >75 nmol/l) |
| Whitehouse et al., 2012 | 473 | - | 5 | Peabody Picture Vocabulary Test | Yes | Children of pregnant women at increased risk when 25(OH)D < 46 nmol/l vs. > 70 nmol/l at 16 weeks gestation |
| Anweiller et al., 2011 | 49 | 76.4 | 7 | Diagnosis of Dementia Alzheiemer's (AD) or Non -AlzheImer's (NAD) | Yes | Increased risk only with NAD when 25(OH)D< 25 nmol/l<br>Small no. of cases of incident dementia |
| MMSE – Mini Mental State Examination, COGTEL [Age quoted as mean] | | | | | | |

5 of 6 longitudinal studies show greater decline in cognition in vitamin D deficient subjects

# Randomised controlled trials Cognition

**Randomised Controlled Trials of Vitamin D and Cognition**

| Author | No. | Population | Length | Age (yrs) | Intervention | Cognitive Outcome | Result / Comment |
|---|---|---|---|---|---|---|---|
| Rossom et al., 2012 | 4143 | Community dwelling females | 7.8 years | > 65 | 400 IU D3 /day + Calcium<br>Placebo | Incident dementia & mild cognitive impairment | No effect<br>Low vitamin D dose<br>Poor compliance |
| Lewellyn et al., 2011 | 120 | Moderate dementia (MMSE 10-20)<br>Not on dementia drugs | 43 weeks | 84.7 | 100,000 IU D3/ month + memantine<br>Placebo/ month + memantine | MMSE, FAB,<br>Trail making A&B,<br>ADAS Cog | Positive effect |
| Dean et al., 2011 | 128 | Healthy adults in Queensland | 6 weeks | 21-22 | 5000 IU D3 /day | Visuospatial working memory (N-Black test)<br>Mental flexibility | No effect<br>High baseline 25(OH)D |
| Stein et al. 2011 | 16 | Community dwelling<br>Mild /moderate AD (MMSE 12-24) | 16 weeks | > 60 | 1000 IU D3/ day throughout and after 8 wks randomised to either:<br>1.7000 IU D3 + nasal insulin/day<br>2. Placebo + nasal insulin /day | ADAS-cog<br>WMS logical memory<br>Disability Assessment in Dementia | No effect |

MMSE –Mini Mental State Examination, FAB –Frontal Assessment Battery, ADAS Cog -Alzheimer's Disease Assessment Scale, WMS – Weschler Memory Scale, AD –Alzheimer's Disease

Only 1 of 4 RCTs showed a positive effect

# Vitamin D and Mood

- Depression has a seasonal variation
  - Higher in Winter when vitamin D levels are lower
- Summer sunlight has been found to increase brain serotonin levels at least twice as much as winter sunlight (Lambert et al., 2002)
- Vitamin D can regulate catecholamine levels (Eyles et al., 2013).

# Cross sectional studies - Mood

| Cross Sectional Studies of 25(OH)D and Mood | | | | |
|---|---|---|---|---|
| **Author** | **No** | **Measure** | **Risk** | **Comments** |
| Hoang et al., 2011 | 12594 | CES-D (short form) | Yes | Not significant in those without prior history of depression |
| Kjaergaard et al., 2011 | 10086 | SCL-10 | Yes | Stronger association in females |
| Ganji et al., 2010 | 7970 | DIS | Yes | Risk when 25(OH)D < 50 nmol/l |
| Brandebarg | 4101 | CES-D | Yes | Pregnant women, risk when 25(OH)D < 74.5nmol/l |
| Jaddou et al., 2011 | 4002 | DASS21 | Yes | Reduced risk significant when 25(OH)D >105 nmol/l |
| Zhao et al., 2010 | 3916 | PHQ-9 | No | Negative only in fully adjusted model |
| Lee et al., 2010 | 3369 | BDI-II | Yes | Risk reduced with rising 25(OH)D from <39.0 to >78.4 nmol/ |
| Pan et al., 2009 | 3262 | CES-D | No | Non significant only after adjusting for location |
| Stewart et al, 2010 | 2070 | GDS | Yes | Risk when 25(OH)D <25 nmol/l |
| Hoogendik et al., 2008 | 1282 | CES-D | Yes | |
| Chan et al., 2011 | 939 | GDS | Yes | Risk comparing <63 nmol/l versus > 92nmol/l |
| Nanri et al., 2009 | 527 | CES-D | No | |
| CES-D Center for Epidemiological Studies Depression scale, SCL-10 –Symptom Checklist Depression Scale -10, DASS-21- Depression, Anxiety Stress Scale -21, BDI- Beck Depression Inventory, GDS – Geriatric Depression Scale, PHQ-9 - Patient Health Questionnaire –9. | | | | |

| Cross Sectional Studies of 25(OH)D and Mood | | | | |
|---|---|---|---|---|
| **Author** | **No** | **Measure** | **Risk** | **Comments** |
| Cassidy Bushrow, et al., 2012 | 178 | CES-D | Yes | Pregnant women, results suggest that risk when 25(OH)D<50 nmol/l |
| Eskandari et al, 2007 | 133 | Psychiatric Assessment | Yes | Case control study |
| Kwasky et al., 2012 | 139 | BDI | No | |
| Brouwer Brolsma et al., 2012 | | GDS | No | No relationship when 25(OH)D rising forom <34 nmol/l to 52-152 nmol/l |
| Bossola et al., 2010 | 80 | BDI II (Italian version) | No | Subjects on dialysis |
| Wilkins et al., 2006 | 80 | DSI | Yes | Risk when 25(OH)D < 25 or 50 nmol/l |
| Armstrong et al., 2007 | 75 | HADS | Yes | Subjects with fibromyalgia – outcome was anxiety |
| Jorde et al., 2006 | 84 | BDI | Yes | Lower BDI when 25(OH)D below 50 nmol/l |
| Sneider et al., 2000 | 60 | Psychiatric Assessment | Yes | Case control study |
| Knippenberg et al., 2013 | 59 | HADS, | No | Subjects with multiple sclerosis, no association in full mdoel |
| Michelson et al., 1996 | 48 | Psychiatric Assessment | No | Case control study |
| Herran et al., 2000 | 38 | Psychiatric Assessment | No | Case control study |
| CES-D – Center for Epidemiology Depression Scale, BDI-Beck Depression Inventory, GDS – Geriatric Depression Scale, HADS – Hospital Anxiety Depression Scale, DSI – Depression Symptoms Inventory. | | | | |

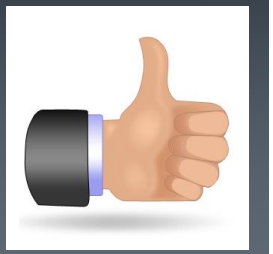
15/24 studies show inverse association between vitamin d levels and mood

# Cohort Studies - Mood

| Longitudinal Studies of 25(OH)D | | | | | | |
|---|---|---|---|---|---|---|
| **Author** | **No.** | **Age** | **Duration** | **Measure** | **Risk** | **Comments** |
| May et al., 2010 | 7538 | 73.1 | 1 yr | ICD-10 | Yes | No adjustment for season |
| Maddock et al., 2013 | 7401 | 45.0 | 5 yrs | MHI | Yes | Risk when <50 or 85 nmol/L |
| Tolapannen et al., 2012 | 2752 | 9.8* | 4 yrs | MFQ | Yes | Outcome measure was only depressive symptoms |
| Milaneschi et al., 2013 | 1596 | 18-65 | 2 yrs | DSM - IV | Yes | OR 0.90 |
| Milaneschi et al., 2010 | 954 | 75.0 | 3-6 yrs | CES-D ≥ 16, CES-D. | Yes | Risk when < 50 nmol/l for both outcomes except in males at 6 yrs, |
| Chan et al., 2011 | 629 | > 65 | 4 yrs | GDS > 8 | No | Small number of cases of incident depression |

MHI – Mental Health Inventory, MFQ – Mood & Feelings Questionnaire, CES-D – Center for EpidemiologIcal Studies Depression Scale, GDS – Geriatric Depression Scale, ICD-10 – International Classification of Diseases -10, DSM IV – Diagnostic Statistical Manual IV. [Age quoted as mean, range or median]

5/6 longitudinal studies showed an increased risk of developing depression when vitamin d levels were low

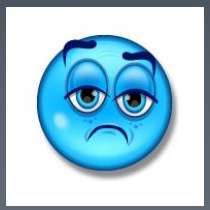


# Randomised controlled trials Mood

| Intervention Trials involving serum 25(OH)D and Mood | | | | | | |
|---|---|---|---|---|---|---|
| **Author** | **No.** | **Duration** | **Treatment** | **Measure** | **Effect** | |
| Bertone-Jonhston et al., 2012 | 2263 | 2 years | 400 IU D3 +1000 mg Ca /day* | Burnam Scale / Antidepressant use | No | Low dose of vitamin D |
| Sanders et al., 2011 | 2012 | 3-5 years | 500,000 IU D3 stat /year | GHQ, SFHS, others | No | Few had 25(OH)D < 25 nmol/l |
| Drumville et al., 2006 | 912 | 6 months | 800 IU D3 + 1000 mg Ca / day | MCS | No | |
| Yalamanchilli et al.,2012 | 489 | 3 years | $1,25(OH)_2D3$ + HRT | GDS | No | |
| Jorde et al., 2008 | 441 | 1 year | 20,000 or 40,000 IU D2 / wk | BDI | Yes | Drop out rate 25%, small decrease in BDI |
| Harris et al., 1993 | 250 | 12 month | 400 IU D2 + 337 mg Ca / day | PMQ | No | |
| Dean et al., 2011 | 128 | 6 weeks | 5000 IU D3 /day | BDI, STAI | No | High baseline vitamin D |
| Vieth et al., 2004 | 82 | 6 months | 4000 IU or 600 IU D3 / day | Well being score | Yes | No difference with higher dose |
| Mozaffari-Khosravi et al., 2013 | 80 | 3 months | 300,000 /100,000 IU D3 stat | BDI-II | Yes | Higher dose more effective |
| Kenny et al., 2003 | 65 | 6 months | 1000 IU D3 + Ca / day | Health perception | No | |
| Hogberg et al., 2012 | 48 | 3 months | | WHO wellbeing scale, MFQ-S | Yes | Improvement in several domains |
| Landsdowne et al.,1998 | 44 | 5 days | 400 IU or 800 IU D3 / day | Self Report Measure of Affect | Yes | |
| Khoraminya et al., 2013 | 40 | 8 weeks | 800 IU D3 + Fluoxetine or placebo | HDRS, BDI | Yes | Vitamin D with SSRI better |
| Partonen et al., 1996 | 29 | 2 weeks | Bright light | Depressive Symptoms | No | |
| Gloth et al., 1999 | 15 | 1 month | 100,000 IU D3 stat | HDS | Yes | |
| Shipowick et al., 2009 | 6 | 8 weeks | 5000 IU D3 daily | BDI -II | Yes | |

GHQ – General Health Questionnaire, SHFS- Short Form Health Survey, PGIIS –Patient Global Impression Improvement Scale, STAI – Strait Anxiety Inventory, HDRS – Hamilton Depression Rating Scale ,WHO –World Health Organisation.

8/16 RCTs positive



# Vitamin D vs Cognition & Mood

- Reasonable observational associations between low vitamin d levels low mood and impaired cognition
- Poor and limited evidence of effect of vitamin d supplementation
- Observational studies very heterogenous
  - Many populations not vitamin d deficient
  - Use of insensitive or limited measures
  - Dementia not always excluded
  - Inadequate controlling for confounds (sun exposure, supplement use)
  - Inadequate controlling for frailty (reverse causality)

# Tuda Study

- Very large homogenous population (3 Irish community dwelling cohorts aged 60 or over - > 5,000 subjects)
- Disease specific cohorts allowing over representation of certain diseases
- Neuropsychological test battery - very sensitive measure of cognitive impairment
- Dementia excluded – early effects can be studied
- Diet, supplement use and solar radiation exposure all recorded

# Tuda study

- Community dwelling patients > 60 years
- MMSE <16 or clinical dementia excluded
- 3 cohorts
  - Mild Cognitive impairment
    - <1.5 sd in at least 1 cognitive domain on neuropsychological testing
  - Osteopaenia
    - T score < 1 sd
  - Hypertension
    - BP >140/90 and/or on anti-hypertensive meds

# Tuda and Cognition

- MMSE <24 excluded

- Hypertensive cohort 1568
- Bone cohort 1330
- Cognitive cohort 1199

- Significant interaction terms between vitamin d cognition and cohort (all $p<0.0001$) so cohort analysed separately

# Tuda and Mood

- Mood assesses using Centre for Epidemiologic Studies Depression scale (CES-D)
- Mood analysed both continuously (CES-D score) and dichotomously (CES-D score ≥16 indicating major depression)

- MMSE <24 excluded

- Hypertensive cohort 1568
- Bone cohort 1330
- Cognitive cohort 1199

- Significant interaction terms between vitamin d CESD score and cohort (all $p<0.0001$) so cohort analysed separately

# Vitamin D and Cognition/Mood

- Strong independent associations between vitamin d and specific cognitive domains seen in some but not all of the cohorts
- Strong independent associations between vitamin d and mood seen in some but not all of the cohorts

# Implications

- Vitamin D associations are more complex than heretofore suspected.
- Vitamin D levels seem to be associated with mood and executive dysfunction in patients with intact cognition
- Associations were seen across all quintiles of Vitamin D level