PRIORITY BRIEFING

The purpose of this briefing paper is to aid Stakeholders in prioritising topics to be taken further by PenCLAHRC as the basis for a specific evaluation or implementation research project. They were complied in 2-3 days.

Can vitamin D supplements be used to prevent dementia and cognitive decline in older adults with mild to moderate cognitive impairment?

Question ID: 3
Question type: Intervention
Question: Can vitamin D supplements be used to prevent dementia and cognitive decline in older adults with mild to moderate cognitive impairment?

Population: Vitamin D deficient adults aged 65 years and older with mild to moderate cognitive impairment living in the southwest.

Intervention: Previous studies have established that vitamin D supplementation is a safe, effective and inexpensive way to reduce vitamin D deficiency and improve health outcomes. We therefore aim to conduct an RCT to establish whether vitamin D supplements can be used to improve the health outcomes of people with mild to moderate cognitive impairment. The study will involve four key stages: 1) Review the literature on vitamin D trials in the elderly in order to further develop the trial protocol. 2) Conduct a series of patient public involvement focus groups with patients and their carers in collaboration with Andy Gibson (PenCLAHRC) to inform the study design and ensure that materials for patients/carers and outcome measures are appropriate. 3) Conduct a multicentre pilot RCT to assess the feasibility and effectiveness of oral vitamin D supplementation in older adults with mild to moderate cognitive impairment. 4) Develop a protocol for funding by the NIHR for a large-scale RCT. This will involve a larger number of memory clinics nationally and a follow-up period of several years.

Control: Given that vitamin D supplementation is likely to be effective and improve patients' health outcomes it may be unethical to withhold treatment and conduct a placebo controlled trial. We are therefore considering an additional active treatment arm where patients receive a low dose of vitamin D in line with the current recommended daily allowance (details to be finalised).

Outcome: The main aims of the study are to evaluate whether vitamin D supplementation is effective at optimising vitamin D levels (Serum 25-hydroxyvitamin D levels - target level >75 nmol/L) in older adults with cognitive impairment, and whether supplementation helps to prevent dementia and cognitive decline assessed by standardised neuropsychology tests) and to determine development of all-cause dementia. Secondary outcomes include: total mortality, falls and fractures, functional disability, health conditions (particularly stroke, cardiovascular disease and type 2 diabetes),

institutionalisation, participant wellbeing (including depressive symptoms) and caregiver wellbeing (including depressive symptoms and caregiver strain).

Dementia: Dementia is a common condition characterised by loss of cognitive functions such as memory and problem solving beyond what would be expected from normal ageing. The diagnosis of dementia also requires that the person's cognitive functions have declined to the extent that it interferes with their work, social activities, self-care or relationships with others. Treatment options that are currently available are largely limited to treating symptoms such as difficulties in maintaining attention. For the majority of people with dementia there is currently no treatment that will alter the course of the disease. Mild/moderate cognitive impairment (MCI) describes those who have deficits in one or more cognitive domain, such as memory, that has not progressed to the degree that they have dementia and daily activities become difficult.

Vitamin D: Vitamin D is a fat-soluble vitamin that can be stored in the body for long periods. Vitamin D is mainly produced by the body when skin is exposed to ultraviolet (UV) rays (just 20 minutes in the sun can stimulate enough vitamin D synthesis within the body to maintain healthy (adequate) levels), though some foods such as oily fish contain moderate amounts. In some countries, such as the US, staple foods like milk are fortified with vitamin D, and supplements are also widely available. Vitamin D is essential for calcium absorption which is important for bone strength and density, it has a known role in the prevention of rickets and osteoporosis. Vitamin D also has a part to play in immune function and muscle strength.

As we age our skin becomes less able/efficient at synthesising Vitamin D and so we are left open to more risks of deficiency which can lead to brittle bones and muscular weakness. Vitamin D deficiency is typically defined as a serum 25-hydroxyvitamin D [25(OH)D] level of less than 50 nmol/L (20ng), and insufficiency as less than 75 nmol/L (30ng). However, there is some variability between studies regarding the level of defined deficiency and its measurement[1]. Some studies report less than 10ng/ml (25nmol/L) as deficient and less than 20ng/ml (50nmol/L) as insufficient. Agreement over the definition of Vitamin D levels may be required in the current project. Levels of Vitamin D more than or equal to 200ng/ml (500nmol/L) are potentially toxic.

[1] nmol/L this is the measuring unit for vitamin D concentration it stands for nanomoles per litre- a nanomole is one billionth of a mole; ng – nanograms are one billionth of a gram and measure weight; IU – International Unit varys according to the substance as it measures biological activity.

The Health Problem

Dementia and cognitive impairment are common in older adults, although their underlying causes remain largely unclear. Over 21% of the rapidly growing population in the South West is of retirement age or over, and the region is a popular retirement destination. It is estimated that around 15,000 people in Devon currently have dementia, although this is expected to rise to 20,000 people by 2020.The National Dementia Strategy states that there are currently 700,000 people in the UK with dementia costing the economy £17 billion a year. Over the next 30 years the number of people with dementia in the UK will double to 1.4 million, with costs reaching over £50 billion a year. There is an urgent need to identify well tolerated and cost-effective disease-modifying interventions. It is possible that a substantial proportion of cognitive decline and dementia could be prevented which would have an enormous impact on individuals at risk, their carers, family and society as a whole.

Vitamin D deficiency is also very common in older adults and is associated with a greater risk of cognitive decline[14], one study has found that people aged over 65 years with the lowest levels of vitamin D in their blood (8-30 nmol/L) were more than twice as likely to be cognitively impaired than those with the highest levels (66-170 nmol/L).[8] Vitamin D may help to prevent neurodegeneration as it plays an important role in the expression of neurotrophic factors (factors relating to the nervous system), neurogenesis (creation of nerve cells), calcium homeostasis, detoxification and amyloid-beta clearance (reduction of amyloid plaques in the brain). 50-60% of young women and men (19- 24 years) in the UK are reported by the Scientific Advisory Committee for Nutrition (SACN, 2007) to have low vitamin D status (<40nmol/L) and around a third have less than 25nmol/L. In the older population levels of vitamin D vary greatly between those who are institutionalised and those who are not. SACN report that 20-55% of adults aged over 65 years and not in an institution have less than 40nmol/L (the percentage increases with age) this is between 70-87% in institutionalised adults over 65years. For those with less than 25nmol/L the figures are reported as 5-25% of non-institutionalised adults and 36-43% of institutionalised adults over 65 years. Recent research has revealed that vitamin D deficiency is also associated with a greater risk of stroke, cardiovascular disease, type 2 diabetes and mortality.[2]

Supplementation is reported to be well-tolerated, effective and inexpensive and reduces the risk of falls, fractures (as a result of falling) and mortality. Few foods naturally contain vitamin D and because the UK is located at high latitude (54° N) vitamin D synthesis from sunlight is limited from November to February (National Institute of Health (US). In the summer months complete cloud cover reduces UV energy by 50%; shade (including that produced by severe pollution) reduces it by 60%. Exposure to sunshine indoors through a window does not produce vitamin D. Sunscreens with a sun protection factor of 8 or more appear to block vitamin D-producing UV rays, although in practice people generally do not follow

[2] This information was obtained from the question submission, which listed the following brief references Poole et al., 2006; Wang et al., 2008; Pittas et al 2006; Melamed et al, 2008; and Autier and Gandini, 2007

application requirements optimally. Skin therefore is likely to synthesise some vitamin D even when it is protected by sunscreen. Data from the UK National Diet and Nutrition Survey suggest that on average the whole of the UK population has blood Vitamin D levels below 75nmol/L throughout the year. What is more, because skin becomes less efficient at producing vitamin D from sunlight with age, many community-living older men (50%) and women (62%) in England are estimated as being vitamin D deficient, as are most institutionalised adults (81%).

Guidelines:
NICE guidelines *Supporting people with dementia and their carers in health and social care* (2006) do not mention Vitamin D as a potential modifiable risk factor in the prevention of dementia or cognitive decline. There are no research recommendations for the investigation of vitamin D.

NHS Priority
Regional
SW SHA Priorities framework 2008-11

- falls prevention and bone health programmes to reduce emergency admissions as a result of falls
- personalised care plan to support self-management
- people diagnosed with dementia to have an initial agreed care plan within four weeks of diagnosis.

Local
Local perspective

- earlier diagnosis and prevention of dementia (CPCT)
- better prevention and earlier intervention in mental health services (DPCT and Plym)
- Promote independence and at home care in dementia (CPT)

Existing Research

Published research
One systematic review was retrieved, conducted in 2009, synthesising studies of Vitamin D and Cognitive performance in adults from 1979 to 2008.[1] This review concluded that the association between Vitamin D and cognitive performance is not yet clearly established due in part to lack of sufficiently powerful research methods. The review found no RCTs or prospective cohort studies and of the 99 studies found only five observational studies were included in the review. Since this review, a number of other reviews[2,3,4,7] and primary research studies[5,6,8-12] have been conducted. Most of the current evidence follows a trend towards an association between vitamin D and cognitive function but the research methods could be stronger. Most recent primary research studies have been cross-sectional and have identified an association between low vitamin D status and

cognitive function. However, there has been one prospective study conducted between 1998-2006[13] (in press) which followed 868 adults aged 65 years and older for six years. This study reports also supports the association of Vitamin D deficiency with cognitive function.

Ongoing Research:
There are currently two ongoing research projects relevant to this area. The University of Western Australia is conducting an RCT on the impact of Vitamin D supplementation on cognitive decline of people with mild cognitive impairment and low Vitamin D levels (50-12.5nmol). The trial aims to recruit 110 participants aged 65 years and older. Participants will receive 1000IU of vitamin D daily for 18 months. Cognitive decline, development of dementia, depression, quality of life, walking speed, lower limb strength, balance, weight, fear of falling and activity levels will all be measured at 18 month follow-up (some outcomes will also be measured at 6 and 12 month follow-up). This study (VITA-D) began in 2007 and is due to complete at the end of April this year (2010), analysis will begin in May 2010 working towards a publication.

The University of Miami is examining the safety of two doses of Vitamin D supplementation (400IU v. 2000IU daily) over six months. However, they are only looking at physiological safety and physical performance outcomes. This study began in 2008 and was due to be completed in April 2009.

Feasibility:
Blood tests are routinely used by memory clinics to exclude potentially reversible causes of dementia including vitamin B12 deficiency, hypothyroidism, diabetes and disorders of calcium metabolism. Testing vitamin D levels could therefore be added into this diagnostic process at minimal inconvenience to clinicians. Vitamin D supplements could then be incorporated into the care plan of older adults with cognitive impairment who were vitamin D deficient.

Key stakeholders, including clinicians, patients, and caregivers, will be engaged at all stages of this project, which will improve the potential of our findings to influence preventive health care in the Peninsula and beyond.

Several clinicians involved in local memory clinics in the southwest have helped to develop this application, and are interested in evaluating whether vitamin D supplementation can be incorporated into the care plan of older adults with cognitive problems.

References

(1) Annweiler, C., G. Allali, et al. (2009). "Vitamin D and cognitive performance in adults: a systematic review." European Journal of Neurology 16(10): 1083-9. Chronic low serum 25-hydroxyvitamin D (25OHD) concentrations are common in adults and are associated with numerous non-skeletal diseases. Vitamin D receptors (VDR) are located in the human cortex and hippocampus, which are key areas for cognition. The objective of this study was to systematically review all published data from the past 30 years which examined the association between serum 25OHD concentrations and cognitive performance in adults. An English and French Medline, PsycINFO and Cochrane Library search ranging from 1979 to 2008 indexed under the Medical Subject Heading (MeSH) terms 'Vitamin D' or 'Hydroxycholecalciferols' combined with the terms 'Dementia' or 'Cognition' or 'Cognition Disorders' or 'Delirium' or 'Memory' or 'Memory Disorders' or 'Orientation' or 'Executive Functions' or 'Attention' or 'Brain' or 'Neuropsychological Tests' was performed. Of the 99 selected studies, five observational studies met the selection criteria and were included in the final analysis. No prospective cohort study was found. The number of participants ranged from 32 to 9556 community-dwelling older adults (45-65% women). Three studies showed four significant positive associations between serum 25OHD concentrations and global cognitive functions, whereas three other studies exploring specific aspects of cognition showed 11 non-significant associations. This systematic review shows that the association between serum 25OHD concentrations and cognitive performance is not yet clearly established. The inconclusive results of the reviewed studies could be due to methodology, types of the cognitive tasks used and/or the cellular mechanisms of vitamin D.

(2) Buell, J. S. and B. Dawson-Hughes (2008). "Vitamin D and neurocognitive dysfunction: preventing "D"ecline?" Molecular Aspects of Medicine 29(6): 415-22. A preponderance of evidence supports a role for vitamin D beyond the classical function in mineral homeostasis. Epidemiologic investigations have revealed a beneficial role of vitamin D in muscle function, cardiovascular health, diabetes, and cancer prevention. More recently, studies have suggested a potential beneficial role of vitamin D in cognitive function. Vitamin D exhibits functional attributes that may prove neuroprotective through antioxidative mechanisms, neuronal calcium regulation, immunomodulation, enhanced nerve conduction and detoxification mechanisms. Compelling evidence supports a beneficial role for the active form of vitamin D in the developing brain as well as in adult brain function. The vitamin D receptor and biosynthetic and degradative pathways for the hydroxylation of vitamin D have been found in the rodent brain; more recently these findings have been confirmed in humans. The vitamin D receptor and catalytic enzymes are colocalized in the areas of the brain involved in complex planning, processing, and the formation of new memories. These findings potentially implicate vitamin D in neurocognitive function.

(3) Cherniack, E. P., B. R. Troen, et al. (2009). "Some new food for thought: the role of vitamin D in the mental health of older adults." Current Psychiatry Reports 11(1): 12-9. Vitamin D, a multipurpose steroid hormone vital to health, has been increasingly implicated in the pathology of cognition and mental illness. Hypovitaminosis D is prevalent among older adults, and several studies suggest an association between hypovitaminosis D and basic and executive cognitive functions, depression, bipolar disorder, and schizophrenia. Vitamin D activates receptors on neurons in regions implicated in the regulation of behavior, stimulates neurotrophin release, and protects the brain by buffering antioxidant and anti-inflammatory defenses against vascular injury and improving metabolic and cardiovascular function. Although additional studies are needed to examine the impact of supplementation on cognition and mood disorders, given the known health benefits of vitamin D, we recommend greater supplementation in older adults.

(4) McCann, J. C. and B. N. Ames (2008). "Is there convincing biological or behavioral evidence linking vitamin D deficiency to brain dysfunction?" FASEB Journal 22(4): 982-1001.
Vitamin D insufficiency is common in the United States; the elderly and African-Americans are at particularly high risk of deficiency. This review, written for a broad scientific readership, presents a critical overview of scientific evidence relevant to a possible causal relationship between vitamin D deficiency and adverse cognitive or behavioral effects. Topics discussed are 1) biological functions of vitamin D relevant to cognition and behavior; 2) studies in humans and rodents that directly examine effects of vitamin D inadequacy on cognition or behavior; and 3) immunomodulatory activity of vitamin D relative to the proinflammatory cytokine theory of cognitive/behavioral dysfunction. We conclude there is ample biological evidence to suggest an important role for vitamin D in brain development and function. However, direct effects of vitamin D inadequacy on cognition/behavior in human or rodent systems appear to be subtle, and in our opinion, the current experimental evidence base does not yet fully satisfy causal criteria. Possible explanations for the apparent inconsistency between results of biological and cognitive/behavioral experiments, as well as suggested areas for further research are discussed. Despite residual uncertainty, recommendations for vitamin D supplementation of at-risk groups, including nursing infants, the elderly, and African-Americans appear warranted to ensure adequacy.

(5) Annweiler, C., A. M. Schott, et al. (2010). "Association of vitamin D deficiency with cognitive impairment in older women: cross-sectional study." Neurology 74(1): 27-32.
OBJECTIVE: The association between low serum 25-hydroxyvitamin D [25(OH)D] concentration and cognitive decline has been investigated by only a few studies, with mixed results. The objective of this cross-sectional population-based study was to examine the association between serum 25(OH)D deficiency and cognitive impairment while taking confounders into account. METHODS: The

subjects, 752 women aged > or =75 years from the Epidemiologie de l'Osteoporose (EPIDOS) cohort, were divided into 2 groups according to serum 25(OH)D concentrations (either deficient, <10 ng/mL, or nondeficient, > or =10 ng/mL). Cognitive impairment was defined as a Pfeiffer Short Portable Mental State Questionnaire (SPMSQ) score <8. Age, body mass index, number of chronic diseases, hypertension, depression, use of psychoactive drugs, education level, regular physical activity, and serum intact parathyroid hormone and calcium were used as potential confounders. RESULTS: Compared with women with serum 25(OH)D concentrations > or =10 ng/mL (n = 623), the women with 25(OH)D deficiency (n = 129) had a lower mean SPMSQ score (p < 0.001) and more often had an SPMSQ score <8 (p = 0.006). There was no significant linear association between serum 25(OH)D concentration and SPMSQ score (beta = -0.003, 95% confidence interval -0.012 to 0.006, p = 0.512). However, serum 25(OH)D deficiency was associated with cognitive impairment (crude odds ratio [OR] = 2.08 with p = 0.007; adjusted OR = 1.99 with p = 0.017 for full model; and adjusted OR = 2.03 with p = 0.012 for stepwise backward model). CONCLUSIONS: 25-Hydroxyvitamin D deficiency was associated with cognitive impairment in this cohort of community-dwelling older women.

(6) Buell, J. S., B. Dawson-Hughes, et al. "25-Hydroxyvitamin D, dementia, and cerebrovascular pathology in elders receiving home services." Neurology 74(1): 18-26.
BACKGROUND: Vitamin D deficiency has potential adverse effects on neurocognitive health and subcortical function. However, no studies have examined the association between vitamin D status, dementia, and cranial MRI indicators of cerebrovascular disease (CVD). METHODS: Cross-sectional investigation of 25-hydroxyvitamin D [25(OH)D], dementia, and MRI measures of CVD in elders receiving home care (aged 65-99 years) from 2003 to 2007. RESULTS: Among 318 participants, the mean age was 73.5 +/- 8.1 years, 231 (72.6%) were women, and 109 (34.3%) were black. 25(OH)D concentrations were deficient (<10 ng/mL) in 14.5% and insufficient (10-20 ng/mL) in 44.3% of participants. There were 76 participants (23.9%) with dementia, 41 of which were classified as probable AD. Mean 25(OH)D concentrations were lower in subjects with dementia (16.8 vs 20.0 ng/mL, p < 0.01). There was a higher prevalence of dementia among participants with 25(OH)D insufficiency (< or =20 ng/mL) (30.5% vs 14.5%, p < 0.01). 25(OH)D deficiency was associated with increased white matter hyperintensity volume (4.9 vs 2.9 mL, p < 0.01), grade (3.0 vs 2.2, p = 0.04), and prevalence of large vessel infarcts (10.1% vs 6.9%, p < 0.01). After adjustment for age, race, sex, body mass index, and education, 25(OH)D insufficiency (< or =20 ng/mL) was associated with more than twice the odds of all-cause dementia (odds ratio [OR] = 2.3, 95% confidence interval [CI] 1.2-4.2), Alzheimer disease (OR = 2.5, 95% CI 1.1-6.1), and stroke (with and without dementia symptoms) (OR = 2.0, 95% CI 1.0-4.0). CONCLUSIONS: Vitamin D insufficiency and deficiency was associated with all-cause dementia, Alzheimer disease, stroke (with and without dementia symptoms), and MRI indicators of

cerebrovascular disease. These findings suggest a potential vasculoprotective role of vitamin D.

(7) Grant, W. B. (2009). "Does vitamin D reduce the risk of dementia?" Journal of Alzheimer's Disease 17(1): 151-9.
The understanding of the role of vitamin D in maintaining optimal health has advanced sharply in the past two decades. There is mounting evidence for beneficial roles for vitamin D in reducing the risk of bone diseases and fractures, many types of cancer, bacterial and viral infections, autoimmune diseases, and cardiovascular diseases. Recently, several reports have also been published regarding the role of vitamin D in neuroprotection. This article develops the hypothesis that vitamin D can reduce the risk of developing dementia, presenting the evidence from observational and laboratory studies. The observational evidence includes that low serum 25-hydroxyvitamin D [25(OH)D] has been associated with increased risk for cardiovascular diseases, diabetes mellitus, depression, dental caries, osteoporosis, and periodontal disease, all of which are either considered risk factors for dementia or have preceded incidence of dementia. The laboratory evidence includes several findings on the role of vitamin D in neuroprotection and reducing inflammation. Although this evidence is supportive, there do not appear to be observational studies of incidence of dementia with respect to prediagnostic serum 25(OH)D or vitamin D supplementation. Such studies now appear to be warranted.

(8) Llewellyn, D. J., K. M. Langa, et al. (2009). "Serum 25-hydroxyvitamin D concentration and cognitive impairment." Journal of Geriatric Psychiatry & Neurology 22(3): 188-95.
Vitamin D may be of interest in the prevention of cognitive impairment, though previous findings are inconclusive. Participants were 1766 adults aged 65 years and older from the Health Survey for England 2000, a nationally representative population-based study. Cognitive impairment was assessed using the Abbreviated Mental Test Score. The cross-sectional relation of serum 25-hydroxyvitamin D quartiles to cognitive impairment was modeled using logistic regression. In all, 212 participants (12%) were cognitively impaired. Odds ratios (95% confidence intervals) for cognitive impairment in the first (8-30 nmol/L), second (31-44 nmol/L), and third (45-65 nmol/L) quartiles of serum 25-hydroxyvitamin D compared with the fourth (66-170 nmol/L) were 2.3 (1.4-3.8), 1.4 (0.8-2.4), and 1.1 (0.6-1.9), after adjustment for age, sex, education, ethnicity, season of testing, and additional risk factors for cognitive impairment (P for linear trend = .001). Our data suggest low serum 25-hydroxyvitamin D is associated with increased odds of cognitive impairment.

(9) Oudshoorn, C., F. U. S. Mattace-Raso, et al. (2008). "Higher serum vitamin D3 levels are associated with better cognitive test performance in patients with Alzheimer's disease." Dementia & Geriatric Cognitive Disorders 25(6): 539-43.
BACKGROUND/AIMS: Recent studies suggest that vitamin D metabolites may be important for preserving cognitive function via specific neuroprotective effects.

No large studies have examined the association between vitamin D status and cognition. METHODS: In this cross-sectional study, we analyzed the serum 25-hydroxyvitamin D(3) levels and Mini-Mental State Examination (MMSE) test scores of 225 older outpatients who were diagnosed as having probable Alzheimer's disease (AD). In addition to the 25-hydroxyvitamin D(3) levels, we analyzed the serum vitamin B(1), B(6) and B(12) levels. RESULTS: An association was found between MMSE test scores and serum 25-hydroxyvitamin D(3) levels, with a beta-coefficient of 0.05 (p = 0.01). Vitamin-D-sufficient patients had significantly higher MMSE scores as compared to vitamin-D-insufficient ones. No association was found with the other serum vitamin levels. CONCLUSIONS: These data support the idea that a relationship exists between vitamin D status and cognition in patients with probable AD. However, given the cross-sectional design of this study, no causality can be concluded. Further prospective studies are needed to specify the contribution of vitamin D status to the onset and course of cognitive decline and AD.

(10) Slinin, Y., M. L. Paudel, et al. "25-Hydroxyvitamin D levels and cognitive performance and decline in elderly men." Neurology 74(1): 33-41. OBJECTIVE: To test the hypothesis that lower 25-hydroxyvitamin D [25(OH)D] levels are associated with a greater likelihood of cognitive impairment and risk of cognitive decline. METHODS: We measured 25(OH)D and assessed cognitive function using the Modified Mini-Mental State Examination (3MS) and Trail Making Test Part B (Trails B) in a cohort of 1,604 men enrolled in the Osteoporotic Fractures in Men Study and followed them for an average of 4.6 years for changes in cognitive function. RESULTS: In a model adjusted for age, season, and site, men with lower 25(OH)D levels seemed to have a higher odds of cognitive impairment, but the test for trend did not reach significance (impairment by 3MS: odds ratio [OR] 1.84, 95% confidence interval [CI] 0.81-4.19 for quartile [Q] 1; 1.41, 0.61-3.28 for Q2; and 1.18, 0.50-2.81 for Q3, compared with Q4 [referent group; p trend = 0.12]; and impairment by Trails B: OR 1.66, 95% CI 0.98-2.82 for Q1; 0.96, 0.54-1.69 for Q2; and 1.30, 0.76-2.22 for Q3, compared with Q4 [p trend = 0.12]). Adjustment for age and education further attenuated the relationships. There was a trend for an independent association between lower 25(OH)D levels and odds of cognitive decline by 3MS performance (multivariable OR 1.41, 95% CI 0.89-2.23 for Q1; 1.28, 0.84-1.95 for Q2; and 1.06, 0.70-1.62 for Q3, compared with Q4 [p = 0.10]), but no association with cognitive decline by Trails B. CONCLUSION: We found little evidence of independent associations between lower 25-hydroxyvitamin D level and baseline global and executive cognitive function or incident cognitive decline.

(11) Wilkins, C. H., S. J. Birge, et al. (2009). "Vitamin D deficiency is associated with worse cognitive performance and lower bone density in older African Americans." Journal of the National Medical Association 101(4): 349-54. BACKGROUND: Vitamin D deficiency is common in older adults and is more prevalent among persons with darker pigmented skin. The detrimental effects of vitamin D deficiency on the bone are widely known; however, recent data

suggest that vitamin D deficiency may contribute to other disorders, including low mood, cognitive impairment, and impaired mobility. OBJECTIVE: The purpose of this study was to determine whether nonskeletal diseases such as depression, cognitive impairment, and physical disability, which have been associated with vitamin D deficiency, are more commonly seen in older African Americans. DESIGN: In a cross-sectional study of 60 older adults (30 African Americans and 30 European Americans), vitamin D status, cognitive performance, physical performance, and bone mineral density (BMD) were assessed. Differences between groups and differences between those with vitamin D deficiency and those with normal vitamin D levels were tested. RESULTS: African Americans had a lower mean 25-hydroxyvitamin D level (17.98 ng/ml; SD, 6.9) compared to European Americans (25.20 ng/ml; SD, 7.0; $p < .0001$). Participants with vitamin D deficiency performed worse on a measure of cognitive performance, the Short Blessed Test (10.87 vs 6.31; $p = .016$); the Physical Performance Test (PPT) (27.00 vs 28.96; $p = .039$); and had lower BMD (0.823 vs 0.914; $p = .005$) and t scores (-1.29 vs -0.72; $p = .008$) of the hip. Among African Americans, vitamin D deficiency was associated with worse cognitive performance and lower BMD of the hip. CONCLUSIONS: Vitamin D deficiency in older African Americans was associated with worse cognitive performance and lower BMD of the hip.

(12) Wilkins, C. H., Y. I. Sheline, et al. (2006). "Vitamin D deficiency is associated with low mood and worse cognitive performance in older adults." American Journal of Geriatric Psychiatry 14(12): 1032-40.
BACKGROUND: Vitamin D deficiency is common in older adults and has been implicated in psychiatric and neurologic disorders. This study examined the relationship among vitamin D status, cognitive performance, mood, and physical performance in older adults. METHODS: A cross-sectional group of 80 participants, 40 with mild Alzheimer disease (AD) and 40 nondemented persons, were selected from a longitudinal study of memory and aging. Cognitive function was assessed using the Short Blessed Test (SBT), Mini-Mental State Exam (MMSE), Clinical Dementia Rating (CDR; a higher Sum of Boxes score indicates greater dementia severity), and a factor score from a neuropsychometric battery; mood was assessed using clinician's diagnosis and the depression symptoms inventory. The Physical Performance Test (PPT) was used to measure functional status. Serum 25-hydroxyvitamin D levels were measured for all participants. RESULTS: The mean vitamin D level in the total sample was 18.58 ng/mL (standard deviation: 7.59); 58% of the participants had abnormally low vitamin D levels defined as less than 20 ng/mL. After adjusting for age, race, gender, and season of vitamin D determination, vitamin D deficiency was associated with presence of an active mood disorder (odds ratio: 11.69, 95% confidence interval: 2.04-66.86; Wald $chi(2) = 7.66$, $df = 2$, $p = 0.022$). Using the same covariates in a linear regression model, vitamin D deficiency was associated with worse performance on the SBT ($F = 5.22$, $df = [2, 77]$, $p = 0.044$) and higher CDR Sum of Box scores ($F = 3.20$, $df = [2, 77]$, $p = 0.047$) in the vitamin D-deficient group. There was no difference in performance on the MMSE, PPT, or factor scores between the vitamin D groups. CONCLUSIONS: In a cross-section of older

adults, vitamin D deficiency was associated with low mood and with impairment on two of four measures of cognitive performance.

13) Llewellyn, D.J., Lang, I.A., Langa, K.M., Muniz-Terrera, G., Phillips, C.L., Cherubini, A., Ferrucci, L., Melzer, D. (in press). Vitamin D and risk of cognitive decline in the elderly. *Archives of Internal Medicine*.
Background: No prospective study has examined the association between vitamin D and cognitive decline or dementia. Methods: We determined whether low levels of serum 25-hydroxyvitamin D [25(OH)D] were associated with an increased risk of substantial cognitive decline in the InCHIANTI population-based study conducted in Italy between 1998 and 2006 with follow-up assessments every 3 years. 858 adults aged 65 years or more completed interviews, cognitive assessments, medical examinations, and provided blood samples. Cognitive decline was assessed using the Mini-Mental State Examination (MMSE; substantial decline defined as ≥3 points) and the Trail Making Tests A and B (substantial decline defined as worst 10% of the distribution of decline or if testing discontinued). Results: The multivariate adjusted relative risk (95% confidence interval [CI]) of substantial cognitive decline on the MMSE in participants who were severely serum 25(OD)D deficient (<25 nmol/L) in comparison with those sufficient (≥75 nmol/L) was 1.60 (95% CI 1.19 to 2.00). Multivariate adjusted random effects models demonstrated that participants who were severely 25(OH)D deficient declined by an additional 0.3 MMSE points per year more than those who were sufficient. The relative risk for substantial decline on the Trail Making Test B was 1.31 (95% CI, 1.03 to 1.51) among those who were severely 25(OH)D deficient compared with those sufficient. No significant association was observed for the Trail Making Test A. Conclusions: Low levels of vitamin D are associated with substantial cognitive decline in the elderly over a six year period. This raises important new possibilities for treatment and prevention.

14) Lee DM, Tajar A, Ulubaev A, et al. Association between 25-hydroxyvitamin D levels and cognitive performance in middle-aged and older European men. *J Neurol Neurosurg Psychiatry.* May 21 2009
BACKGROUND: Although there is evidence that vitamin D inadequacy may be linked to adverse cognitive outcomes, results from studies on this topic have been inconsistent. The aim of this trial was to examine the association between 25-hydroxyvitamin D (25(OH)D) levels and cognitive performance in middle-aged and older European men. METHODS: This population-based cross-sectional study included 3,369 men aged 40-79 years from eight centres enrolled in the European Male Ageing Study. Cognitive function was assessed using the Rey-Osterrieth Complex Figure (ROCF) test, the Camden Topographical Recognition Memory (CTRM) test and the Digit Symbol Substitution Test (DSST). Serum 25(OH)D levels were measured by radioimmunoassay. Additional assessments included measurement of physical activity, functional performance and mood/depression. Associations between cognitive function and 25(OH)D levels were explored using locally weighted and linear regression models. RESULTS: In

total, 3,133 men (mean (+/-SD) age 60+/-11 years) were included in the analysis. The mean (+/-SD) 25(OH)D concentration was 63+/-31 nmol/l. In age-adjusted linear regressions, high levels of 25(OH)D were associated with high scores on the copy component of the ROCF test (beta per 10 nmol/l = 0.096; 95% CI 0.049 to 0.144), the CTRM test (beta per 10 nmol/l = 0.075; 95% CI 0.026 to 0.124) and the DSST (beta per 10 nmol/l = 0.318; 95% CI 0.235 to 0.401). After adjusting for additional confounders, 25(OH)D levels were associated with only score on the DSST (beta per 10 nmol/l = 0.152; 95% CI 0.051 to 0.253). Locally weighted and spline regressions suggested the relationship between 25(OH)D concentration and cognitive function was most pronounced at 25(OH)D concentrations below 35 nmol/l. CONCLUSION: In this study, lower 25(OH)D levels were associated with poorer performance on the DSST. Further research is warranted to determine whether vitamin D sufficiency might have a role in preserving cognitive function in older adults.