Vitamin D & health outcomes

Musculoskeletal health outcomes

Non-musculoskeletal health outcomes

MUSCULOSKELETAL HEALTH OUTCOMES

Rickets

41 studies:

16 case reports 0 reported Ca intake
7 observational 1 reported Ca intake
8 before & after 1 reported Ca intake
7 case control 2 reported Ca intake
3 interventions 1 reported Ca intake; 1 study - both groups received Ca

Table 1: Case reports

ID	Author/year/location/25(OH)D measurement method	Population	Rickets diagnosis	Mean 25(OH)D (nmol/L) & Ca (mg/L) concentrations	Calcium intakes/other comments
1	Iqbal et al (1994) Leicester, UK Competitive protein binding assay	Case 1- Male, age 2 months, presented with hypocalcaemic fits Case 2- Female, age 12 months, presented with failure to thrive	Both had typical appearances of rickets on wrist X-rays.	Case 1: 25(OH)D: <2.5 Adjusted Ca: 43.2 Case 2: 25(OH)D: <5 Adjusted Ca: 84.8	Calcium intakes not reported
2	Train et al (1995) London, UK Method not reported	Two black, exclusively breast-fed infant males. One patient with hypocalcaemic stridor (age 5 m) second patient with respiratory distress (age 7 m)	X-ray examinations confirmed rickets.	Case 1 25(OH)D: <2.5 Ca: 46 Case 2: 25(OH)D: 6 Ca: 36	Calcium intakes not reported
3	Mughal et al (1999) UK	Exclusively breastfed infants (12-24 months) Case 1 – Male, age 21 months Case 2 – Female, age 10 months Case 3 – Female, age 20 months Case 4 – Female, age 15 months Case 5 – Female, age 28 months Case 6 – Female, age 16 months (Country of origin: Palestine, Gambia, Lybia, Saudi Arabia, Iran, Algerian and Lybian)	Clinical signs and symptoms e.g. bow legs, rickety rosary, swelling of the ends of long bones, frontal bossing of the skull, delayed dentition, poor growth and slow motor development. Radiological features e.g. generalised osteopenia, widening of the growth plates, cupping of metaphyseal regions of long bone.	Case 1 – 25(OH)D: 10.7nmol/L, Ca: 1.70nmol/l Case 2 – 25(OH)D: 18.7nmol/L, Ca: 2.17nmol/l Case 3 – 25(OH)D: 3.5nmol/L, Ca: 1.41nmol/l Case 4 – 25(OH)D: 11nmol/L, Ca: 2.17nmol/l Case 5 – 25(OH)D: 14nmol/L, Ca: 2.18nmol/l Case 6 – 25(OH)D: 11.5nmol/L, Ca: 2.18nmol/l	Calcium intake not reported.

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4	Ashraf & Mughal (2002) Manchester, UK	Case 1 – 15 months Case 2 – 8 months Case 3 – 9 months South East Asian ethnicity	Children were examined for deformities and swelling of the metaphyses due to rickets. Children with clinical stigmata of rickets had an x-ray of their left wrist.	Case 1 – 25(OH)D: 25nmol/L, Ca 2.3nmol/L Case 2 – 25(OH)D: 40nmol/L, Ca 2.4nmol/L Case 3 – 25(OH)D: 32.4nmol/L, Ca 2.5nmol/L	Calcium intake not reported.
5	Ladhani et al (2004) London, UK IDS radioimmunoassay	65 children identified with hypocalcaemia or nutritional deficiency rickets (1996-2001) (hospital records of children aged 0-16y at diagnosis of vitamin D deficiency). 39 Asian, 24 Afro-Carribean, 2 Eastern European. 37 males (45%). Age range 0-13 years. Hypocalcaemic children <3 or >10 years. Most rickets cases aged <3 years.	12/29 with hypocalcaemia had radiological evidence of rickets 35/36 without hypocalcaemia had radiological evidence of rickets. Plasma 25OHD <25 nmol/L considered to be vitamin D deficient.	**25(OH)D** median (range) Hypocalcaemic: 5.0 (2.1-14) No hypocalcaemia: 6.7 (2.7-14); p=0.48 **Ca** Hypocalcaemic: (54.4 (33.6-83.2) No hypocalcaemia: 84.4 (52.8-99.6) p<0.0001	Calcium intake not reported. Hypocalcaemia peak in Mar-Jul; rickets presentation throughout year. Symptons reverted to normal in all cases with vit D supplementation
6	Crocombe et al (2004) Manchester, UK	Case 1 – Female, age 13 years Case 2 – Female, age 17 years Case 3 – Female, age 14 years Case 4 – Female, age 11 years Case 5 – Male, age 16 years Case 6 – Female, age 12 years Case 7 – Female, age 15 years Case 8 – Female, age 14 years Case 9 – Female, age 14 years (Country of origin: Iran, India, Afghanistan, Pakistan)	Symptoms of vitamin D deficiency, including lower limb pains, difficulty in walking or climbing stairs, carpopedal spasms, and hypocalcaemic convulsions. Clinical signs included positive Chvostek sign, inability to stand up unaided from a squatting position due to proximal myopathy, bowed legs (genu varum), and knock-knees (genu valgum). Three patients (cases 1, 6, 9) had radiological changes of vitamin D deficiency with widening and fraying of metaphyses, but these changes were not as severe as those seen in toddlers with vitamin D deficiency rickets.	Case 1 - <5nmol/L Case 2 - <5nmol/L Case 3 – 25nmol/L Case 4 – 9nmol/L Case 5 - <5nmol/L Case 6 – 7.5nmol/L Case 7 – 5.5nmo/L Case 8 - <5nmol/L Case 9 - <5nmol/L	Calcium intake not reported.
7	Odeka & Tan (2005) Oldham, UK	3 cases 15-19months	3 children had radiological evidence of rickets.	<25nmol/L	Calcium intake not reported.
8	Kamien & Harris (2007) Perth, Australia Method not reported	2 female twins, Sudanese ethnicity; breast-fed and also received cow's milk, yoghurt, biscuits. At 10 months of age, admitted to hospital with failure to thrive and massive splenomegaly.	For both, x-rays of chest, hand & knee showed clinical rickets: rachitic rosary, large anterior fontanelle, no limb deformities, decreased muscle bulk and tone.	**25(OH)D:** 34 **Calcium:** 88 (Mother's 25(OH)D: 18)	Calcium intake not reported. 2 months after hospital admission, radiology showed good healing of rickets.

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9	Lazol, Cakan & Kamat (2008) Michigan, USA Method not reported	Review of case reports over 10 y with nutritional rickets as primary or secondary diagnosis in Michigan hospital. 58 cases included in study (62% boys) • Mean age 18 months (range 2 to 132m); • 96% born full term; • 81% African American; 14% Arabic	Included only cases where radiological findings supported by laboratory data. Common manifestations of rickets: 74% wide swollen joints, 64% rachitic rosary, 58% bow legs, 36% bone pains, 36% frontal bossing, 31% motor delay, 30% seizures, 25% fractures. Treatment with D2 & calcium (both either orally or intramuscularly)	**25(OH)D:** 79% < 50 33% < 12.5 **Calcium:** Low in 57% Normal in 43%	Calcium intakes not reported. Repeat radiological studies in 17 patients, 1 wk to 30m after diagnosis: > 65% showed evidence of healing rickets; > 29% of near complete resolution of rickets.
10	Williams et al (2008) Boston, USA Diasorin Liaison	1 African American child with rickets diagnosed at well-child appointment. Age = 11 months Treatment 1250 µg (50,000 IU) vitamin D orally/week 50 mg/kg calcium glubionate syrup daily. Follow up at six weeks.	Undetectable 25OHD plus findings of florid rickets from wrist and knee radiographs: osteopenia, minimal fraying of distal ulnar and distal femoral regions and proximal fibular metaphyses.	Before treatment: 25(OH)D: <17.5 Ca: 97 After treatment: 25(OH)D: 250 Ca: 113	Calcium intakes not reported
11	Brown et al (2009) Washington, USA Method not reported	Searched hospital database (1997-2007) for infants with vitamin D deficiency plus dilated cardiomyopathy (DCM). 4 infants (3 male, 1 female) Age: 4-10 months-old Exclusively breastfed; no vitamin D supplementation; African American descent. Treatment Calcium drips and boluses; vitamin D and calcium supplements (dose not specified)	Biochemical laboratory evidence consistent with hypocalcaemic rickets;. All patients had radiographic studies performed and findings for some were consistent with rickets, including rachitic beads on ribs, fraying and cupping of metaphyses, and cardiomegaly.	25(OH)D at diagnosis: Case 1: 13 Case 2: 7 Case 3: 4 Case 4: <13 Ca at diagnosis: Case 1: 58 Case 2: 46 Case 3: 47 Case 4: 63	Calcium intakes not reported. All patients discharged (after 8-19 days] with 'normal serum Ca levels' (no data provided)
12	Holick et al (2009) Mass. USA Method not reported	9 month old boy with generalised seizure and bulging fontanelle. Parents came to USA from East Africa 2 years previously.	Rickets diagnosed on basis of solely breast-fed, unsupplemented infant, presenting with seizure, frontal bossing and bulging fontanelle. Demineralisation present, rachitic rosary & other characteristic radiographic manifestations. Also hypocalcaemia, hypophosphatemia, elevated ALP.	**25(OH)D:** 40	Calcium intakes not reported.

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13	Bhakhri & Debata (2010) New Delhi, India Method not reported	10 month-old infant, born at term, male infant, exclusively breast-fed; Mother did not take supplements during or after pregnancy. Presented with marked pallor, abdominal distension, poor weight gain, delayed development corresponding to 4m old normal infant. Treatment At 10 months of age: oral vitamin D dose of 15,000 µg (600,000 IU) Iron + vitamin B complex supplementation. 11 to 14 months of age: Vitamin D: 71 µg/d (2850 IU); Ca: 500 mg/d	Rickets features: wide-open anterior fontanel, rosary, wrist widening, Harrison sulcus. Diagnosis: rickets with myelofibrosis	At 10 months, 25(OH)D: 22.5 Ca: 72 At 22 months child normocalcemic (no data given). (Mother's 25(OH)D: 15.5)	Calcium intakes not reported. At 11m (after 1m treatment): radiological evidence of healing At 22 months: catch-up in growth (10cm/y), liver not palpable, spleen regressed, normocalcaemic.
14	Akin et al (2010) Kayseri, Turkey Method not reported	23-month-old male patient presenting with recurrent febrile convulsions. Treatment Vitamin D (7500 µg/300,000 IU) + Ca (dose not reported) given orally for 15 days.	Diagnosed as antiepileptic drug-induced Vitamin D deficiency rickets. Mild enlargement of wrists bilaterally. Rachitic rosary, craniotabes, caput quadratum, and leg deformities not present.	Before: 25(OH)D: 11.25 Ca: 64 After treatment: 25(OH)D: not reported Ca: 92	Calcium intakes not reported. Breastfed only until 6m of age then received complementary feeding. Given 10µg (400 IU)/d vitamin D in first 2 months of life.
15	Pearson et al (2010) California, USA Method not reported	16-month-old male toddler: • Hispanic ethnicity • 0-12 months primarily breast-fed; at 12 months weaned onto rice-milk, unfortified with vitamin D or calcium (child had cow's milk allergy) Child presented with weight loss, elevated alkaline phosphatase and PTH	Clinical features of rickets were bow legs and mild frontal bossing. Radiographs consistent with early signs of rickets showed widening & irregular metaphyses of distal femur & proximal tibia.	**25(OH)D** At admission: 3.5 After 5 wks: 27 **Calcium:** Admission: 89 After 5 wks: 90 After 10 wks: 95	**Calcium intakes not reported.** After 12 wks therapy with D3 (25ug/d), multivit & iron supplements, 'child demonstrated significant clinical improvement'.

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16	Brinsmead et al (2011) Brisbane, Australia Method not reported	12 month-old full-term girl; Indian ethnicity, born Australia; fed predominantly breast & cow's milk. 'child's mother had vitamin D and iron deficiencies, with history of poor calcium intake'. Treatment Vitamin D (initially calcitriol, later D2; dose not specified), calcium, iron, vitamin B12, improved diet.	Radiological appearance of wrist and knees consistent with rickets; tender and widened wrists; hypocalcaemia.	At 12 months 25(OH)D: 11.2 Ca: 69 Post-treatment 25(OH)D or calcium not reported. (Mother's 25(OH)D: 21)	Calcium intakes not reported. At 18 months (after 6m treatment): clinical, biochemical and radiological features 'approaching normal'; rapid progression in gross motor development

Table 2: Observational studies

ID	Author/year/location/25(OH)D measurement method	Population	Rickets diagnosis	Mean 25(OH)D (nmol/L) & Ca (mg/L) concentrations	Calcium intakes/other comments
17	Dunnigan et al (1981) Glasgow, UK Competitive protein binding assay	189 Asian children aged 5-17 years in single GP practice. Children grouped depending on vitamin D supplement use: Regular: at least 2x per week, Intermittent: less frequently None: never taking vitamin D supplements.	Diagnosed by GP. No. diagnosed with rickets - radiological signs Regular: 3 (5%) Intermittent: 8 (15%) None: 11 (14%)	**25(OH)D** Regular (n=54): 20.9 (0.76) Intermittent (n=49): 17.48 (0.71) None (n=75): 16.08 (0.57) No. diagnosed with rickets **(**serum Ca <90) Regular: 6 (11%) Intermittent: 16 (30%) None : 31 (39%)	Calcium intakes not reported.
18	Rajah et al (2008) Abu Dhabi, United Arab Emirates Chemiluminescent assay (Nichols Institute Diagnostics)	Retrospective review of patients diagnosed with nutritional rickets (n=31). 16 native Emirati children with a rickets diagnosis: 8 with 25OHD deficiency, 8 with Ca deficiency. Sexes equally represented. Mean age vit D group = 14.79 months ± 3.15 Mean age Ca group = 19.76 months ± 2.31	Any patient with combination of clinical and X-ray features in the presence of elevated alkaline phosphatase. Clinical features included widened wrists, frontal bossing, bowing of the legs and costochondral thickening.	Vitamin D deficiency group: 25(OH)D: 17.27 (4.65) Ca: 91.6 (5.2) Calcium deficiency group: 25(OH)D: 44.30 (17.83) Ca: 93.2 (7.6)	Calcium intakes not reported**.** June 2000-December 2003.
19	Banajeh (2009) Sana'a, Yemen EIA (OCTEIA, IDS)	Prospective cohort study investigating whether rickets predicts outcomes in very severe pneumonia (VSP). 79 children Age: 2 to 59 months	Clinical rickets defined as 2 or more of following signs: rosary beads, craniotabes, frontal bossing, Harrison's sulcus with pigeon chest, wide anterior fontanel, widening of epiphysis, bowing of legs, delay dentition, and double malulous. Child with clinical signs considered rachitic if also had radiological signs of generalized osteopaenia of upper arm bones & widening of costochondral junctions.	**25(OH)D:** 63% (50) >30 37% (29) <30 63% had clinical rickets. Of those with 25(OH)D < 30, 79% rachitic (radiological signs).	Calcium intakes not reported. Study population part of RCT comparing treatments for VSP.
20	Ekbote et al (2010) Pune, India RIA (Diasorin)	111 children (mean age 2.6 years), living in the slums. Group A: 50 'outdoor toddlers' not attending crèche Group B: 61 'indoor toddlers' attending crèche Sunlight exposure (no. of toddlers): Group A: 4<30min; 36>60min Group B: 24<30min;18>60min male/female: Group A: 96/130; Group B: 14/5	Rickets diagnosis based on clinical signs, confirmed by radiographs: delayed closure of fontanel, frontal bossing, dental enamel hypoplasia, rickety rosary, swelling of wrists, knees and ankles, knock knees and bow legs. **Clinical signs of rickets:** Group A: none Group B: 10	Group A: Males: 95.9 (91.6) Females: 130.2 (67.7) 0% <30nmol/L Group B: Males: 14 (32) Females: 5.2 (21.1) 77% <30nmol/L	**Calcium intakes** (median): Group A Males: 216mg/d Females: 218mg/d Group B Males: 292mg/d Females: 251mg/d No difference in mean Ca intake in 2 groups.' Group B children had significantly higher energy and protein intakes.

ID	Author/year/location/25(OH)D measurement method	Population	Rickets diagnosis	Mean 25(OH)D (nmol/L) & Ca (mg/L) concentrations	Calcium intakes/other comments
21	Salama et al (2010) Ain Shams, Egypt I RIA kit	32 breast-fed rachitic infants with 25(OH)D <25nmol/L (20 males) 17 infants with dark skin; 20 exclusively breastfed. 9 infants presented with hypocalcaemic seizures. Mean age of children who presented: With seizures: 3.67 months ± 1.6 Without seizures: 12.35 months ± 4.3 (p=0.001)	Clinical presentation, biochemical results and radiological findings (wrists, knees and ankles).	Children who presented with seizures: 25(OH)D: 24.33 ± 14.75 Ca: 65 ± 14.8 Children who presented without seizures: 25(OH)D: 43.5 ± 20.58 Ca : 85±15 25(OH)D & Ca significantly lower in children with seizure	Calcium intakes not reported
22	Perez-Rossello et al (2011) Boston, USA Chemiluminescence assay (Liason, DiaSorin)	40 children (age 8 – 24 months) with 25(OH)D <50 nmol/L identified from prospective sample of children seen for routine clinical care.	Radiographs from wrists and knees scored for rachitic changes on 10-point Thacher score (and 5-point demineralisation scale). 2 children identified as rachitic.	2 children with rachitic changes 25(OH)D: 9 Ca: 103 34 children without rachitic changes 25(OH)D: 17 Ca :104 Remaining 4 children could not be categorised.	Calcium intakes not reported
23	Munns et al (2012) Australia (national) Method not reported	398 children with vitamin D deficiency rickets (25OHD ≤ 50 nmol/L & alkaline phosphatase >229IU/L) and/or radiological rickets. Median age, 6.3 years (range, 0.2–15 years). (55% male) 98% dark/intermediate skin colour; 18% girls partially/completely veiled. 63% born in Africa. (Excluded those with vitamin D deficiency rickets associated with underlying chronic disease & all genetic forms of rickets.)	95 children had wrist x-rays - 71% had rachitic changes.	25(OH)D - median (range): 28 (5–50) Ca - median (range): 95.2 (48.8–117.6) (Values for all subjects, n=398)	Calcium intakes not reported. Rickets presentation demonstrated seasonal variation: 60% cases identified in winter & spring, compared with 40% in summer & autumn.

Table 3 - Before and after studies

ID	Author/yr/location/ 25OHD measurement method	Population	Rickets diagnosis	Treatment	Mean 25(OH)D (nmol/L) & Ca (mg/L) concentrations	Calcium intakes/other comments
24	Elzouki et al (1989) Benghazi, Libya. Competitive binding assay	22 African black children with confirmed rickets admitted for treatment. Median age 15 months (3-24 months) (n=16) 10 males (63%)	Diagnosis of rickets and decision to treat was left to individual physician. Radiograph of wrist obtained.	Daily sun exposure of 1-3 hours at home/hospital (not monitored). After 1-2 weeks sun exposure (median 9 days), given one dose of 15,000 µg (600,000 IU) intramuscular D2.	At diagnosis: 50% with 25(OH)D < 20 (4-65) Most children had elevated Ca concentrations.	Calcium intakes not reported. Patients responded to sunshine exposure (significant increases in vitamin D metabolites) All attained 25(OH)D of 30-140 nmol/L & improved Ca concentrations.
25	Garabedian et al (1983) Paris, France Competitive binding RIA	20 infants & children with rickets & Age (range): 15 patients aged 4-26 months 5 patients aged 4-12 years 60 controls	1 patients admiited to hospital because of overt signs of rickets; in others, rickets discovered during evaluation of pathological states	9 children 50 µg/d (2000 IU) D2 5 children received single dose of 25(OH)D – 10 µg/kg Treatment lasted until rickets healed. 3 patients given calcium infusion	**Pre treatment** 25(OH)D: 10.1 (4.6) Ca: 75 (11) **Post treatment** 25(OH)D: 131.83 (44.1) Ca: 99.5 (6.4)	Calcium intakes not reported. Diagnosis of vitamin D deficiency confirmed by healing of radiographic bone lesions
26	Bhimma et al (1995) Durban, SA. Competitive binding assay	Black children admitted to hospital with rickets. 23 with (privational) rickets; 14 with Ca deficiency; 9 with vitamin D deficiency mean age = 6.1 years (2-12y); 5 female	Rickets diagnosed clinically, radiologically & biochemically. Vitamin D deficient rickets diagnosis on basis of 25OHD < 25 nmol/L + other features of calciopaenic rickets. Dietary Ca deficiency considered in children with evidence of calciopaenic rickets, but normal 25OHD. Hypophosphatemic VDR rickets diagnosed by normal Ca & vit D concentrations and low PO.	125- 250 µg (5000- 10000 IU) D3 plus 500-1000 mg calcium Biochemistry not presented for follow-up	Baseline - vitamin D deficient patients 25(OH)D: 9.25 (8.75) Ca: 83.6 (10.8) Baseline - Ca deficient patients 25(OH)D: 45.5 (10) Ca: 86.4 (11.2)	Calcium intakes not reported.
27	Soliman et al (2008) Doha, Qatar Radioimmunometric assay	All infants and children up to 3y attending growth clinic (n=46). Mean age = 13.1 months ± 1.1.	Clinical manifestations of rickets with: Low serum 25 OHD Elevated ALP Normal or low Ca Normal of low PO_4 High PTH Radiological confirmation of rickets at the distal, ulnar or femoral epiphysis	6 months (or more) of 7500 µg (300,000 IU) intramuscular vitamin D3.	**Before treatment:** 25(OH)D: 11.25 (1.4) Ca: 82.8 (10) **After treatment:** 25(OH)D: 111.25 (9.25) Ca: 97.6 (8)	Calcium intakes not reported. Oct 2003 and Sept 2005

ID	Author/yr/location/ 25OHD measurement method	Population	Rickets diagnosis	Treatment	Mean 25(OH)D (nmol/L) & Ca (mg/L) concentrations	Calcium intakes/other comments
28	Soliman et al (2009) Doha, Qatar Radioimmunomertic assay	40 children with vitamin D deficiency rickets Mean age: 16.1 months ± 4.5 35/40 exclusively breastfed	Clinical manifestations of rickets with: Low serum 25 OHD Elevated ALP Normal or low Ca Normal of low PO_4 High PTH Radiological confirmation of rickets at the distal, ulnar or femoral epiphysis	Vitamin D3 250 µg (10,000 IU)/kg (max 3750 µg/150,000 IU)	**Before treatment:** 25(OH)D: 15.6 (12.3) Ca: 87.6 (7.6) **After treatment:** 25(OH)D: 70.48 (21.8) Ca: 96 (5.6)	Calcium intakes not reported.
29	Ozkan et al (2009) Turkey Competitive binding RIA	Children diagnosed as VDDR, otherwise healthy 21 cases with rickets. Age: 2-24 months; Median age at referral, 7.3 (2-16) m. Mean follow-up :28 ± 2 d	Clinical rickets diagnosed in children with 2 or more of following: craniotabes (in infants > 2m), bilateral widened wrists, frontal bossing, bowing of legs, pathologic fractures, hypocalcemic tetany, hypocalcemic convulsions, Harrison's sulcus. Radiological evidence of rickets by radiography of left wrist included 2 or more of following: generalized osteopenia, fraying & cupping of distal ends of radius or ulna.	All treated with intramuscular single dose (7500 µg/300,000 IU) of D3, and 50 mg/kg/day of elementary calcium lactate administered orally for 10 days.	**Pre treatment** 25(OH)D: 10.53 (4.6) Ca: 58.2 (5.9) **Post treatment** 25(OH)D: 131.83 (44.1) Ca: 99.5 (6.4) Ca & 25OHD significantly higher post treatment.	Calcium intakes not reported Infants with familial forms of rickets & those with secondary VDD due to kidney, liver & GI system diseases were excluded from study.
30	Thacher et al (2009) Jos, Nigeria. Isotope-dilution liquid chromatography tandem mass spectrometry on an API 4000 instrument	17 prepubertal children with clinical signs of rickets (6 male, 11 female) Mean age (m) (range):44.5 (28–118) Familial rickets Total: 8 (47%) D2: 4 (44%) D3: 4 (50%)	Subjects required radiological score of at least 1.5 on a previously validated 10-point scale for assessing severity of childhood rickets (Thacher et al, see Annex 1)	Baseline study - typical Nigerian meal of maize porridge (150ml) & orange juice (50ml) with added 120 mg Ca (as calcium glubionate) & 20g Ca (as calcium chloride). After drawing blood, 0.5 mg Ca infused slowly. 4d after baseline study, given single oral dose of vitamin D2 or D3(1250 µg (50,000 IU). 3d later (1 wk after baseline study), Ca absorption determined again.	Baseline**:** **25(OH)D** **(**n=2 with 25(OH)D< 30) All: 50 (12.5–80) D2: 45 (25 –80) D3: 57 (31–80) **Ca** All: 88 ± 10 D2: 86 ± 11 D3: 90 ± 10 Increase in 25(OH)D equivalent after D3 (72 ± 25 nmol/L) or D2 (72 ± 42 nmol/L).	Calcium intakes (mg): 182 (73) Serum 25OHD unrelated to reported daily sun exposure.

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31	Cesur et al (2011) Van, Turkey HPLC	Retrospective study of medical records of patients with nutritional rickets (n=946). Inclusion criteria: under 16y; 25(OH)D <25 nmol/L; clinical or radiological signs of rickets. 0-23 month: 51.4% 24 months – 5.9y: 9.2% 6–11.9 years: 17.3% 12-15 years: 22.1%	**Symptoms** Rachitic rosary: 312 Harrison sulcus: 93 Graniotabes: 109 Widening hand wrist: 409 Curvatures of femur, tibia, fibula: 38	1) 3750 µg (single dose); 2) 7500 µg (single dose); 3) 40 µg/d for5- 6 months; 4) 110 µg/d for 3 months.	<u>On admission</u> 25(OH)D: 15 (post-treatment 25(OH)D not reported) <u>Calcium before/after treatment:</u> 0-23 m: 86/87 24m-5.9y: 86/86 6-11.9y: 87/93 12-15y: 88/91	Calcium intakes not reported.

Table 4 - Case control studies

ID	Author/year/location/25(OH)D measurement method	Population	Rickets diagnosis	Mean 25(OH)D (nmol/L) & Ca (mg/L) concentrations	Calcium intakes/other comments
32	Arnaud et al (1976) North Midwestern USA and Canada & Competitive protein binding assay	9 children with nutritional deficiency rickets (7 males; 2 females) Age: 2- 42 m 9 age-matched control infants were outpatients with problems unrelated to skeletal disease.	Rachitic control patients: 6 untreated infants with familial hypophosphataemic rickets established through family history in 5 infants and failure to respond to 125 µg (5000 IU)/day	**25(OH)D** Normal control patient: 90 (30) Mild deficiency (n=2): 45 (7.5) Moderate (n=5): 30 (5) Severe (n=1): 20 Rachitic control mean (n=6): 90 (37.5) **Ca** Normal control patient: 101 (4) Moderate (n=5): 96 (6) Rachitic control mean: 99 (2)	Calcium intake not reported. Specimens from patients with mild rickets obtained mid-winter; from patients with moderate & severe rickets obtained when more sun exposure possible. Healing of bone lesions and normalization of serum CA, P and alkaline phosphatase in nutritional rickets patients.
33	Oginni et al (1996) Ile-Ife, Nigeria IDS radioimmunoassay	26 patients with active rickets (13 female) Age 1-5 years 90 healthy control subjects from the same age and community group (35 males).	Clinical criteria for rickets included swollen wrists, rachitic rosaries and angular deformities of the knees, widening and cupping of the metaphysis, fraying and thickening of the physis and generalized rarefaction	Control patients 25(OH)D: 69 (22) (n=20) Ca: 94 (9.2) (n=26) Rickets patients 25OHD: 36 ± 28 (n=22) Ca: 82.4 ± 9.2 (n=22) **albumin corrected calcium* 25OHD & Ca significantly lower in rachitic children	Calcium intakes not reported.
34	Majid Molla et al (2000) Kuwait radioimmunoassay	103 patients with clinical features of rickets. Mean age: 14.5 (5.2) months 102 age and sex matched controls. Mean age 15.2 96.28) months (not significantly different).	Clinical criteria for rickets: hypotonia, skeletal deformity (bowing of the legs, deformity of the end of the long bones), rachitic rosary, delayed closure of the fontanel, delayed walking and delayed dentition.	Rickets patients 25(OH)D: 26.5 (15.5) Ca: 89.6 (11.2) **Control patients** 25(OH)D: 83.5 (74.75) Ca: 98 (6) Serum 25OHD & Ca significantly lower in rachitic children	Calcium intakes not reported. 8% of patients and 70% of controls were formula-fed.
35	Thacher et al (2000) Jos, Nigeria Radioimmunoassay	123 children with symptoms of rickets Age: 1-14y Rickets: 68 female Controls: 61 female 123 age, weight and sex-matched controls from same community with no sign of rickets (subjects not >5 years not weight-matched so as not to select under-nourished controls).	Rickets diagnosed through evidence of bone deformity: knock knees, bow legs or enlarged wrists.	Means (SD) or median (25^{th} and 75^{th} centiles). Rickets patients 25(OH)D: 32 (22-40) Ca: 77.2 (8.8) Control patients 25(OH)D: 50 (42-62) Ca: 89.6 (6) **albumin corrected* Serum 25OHD & Ca significantly lower in rachitic children.	Calcium intake (mg): Rickets patients: 217 (88) Control patients: 214 (77) Subjects sun exposure was not significantly different. Mean calcium intake below NIH recommendation in both groups

ID	Author/year/location/25(OH)D measurement method	Population	Rickets diagnosis	Mean 25(OH)D (nmol/L) & Ca (mg/L) concentrations	Calcium intakes/other comments
36	Al-Mustafa et al (2007) Al-Khobar and Dammam, Saudi Arabia Competitive protein-binding assay	Children clinically diagnosed with rickets (n=61) were age- and sex-matched with controls (n=58). Controls - children without clinical rickets attending hospital for other blood investigations. Mean age Rachitic group (61% female) - 14.8 months Controls (55% female) - 16.5 months	Clinical diagnosis; no other detail.	Rickets **25(OH)D** 75% <20 25% >20 **Calcium**: 31% <21.25 59% 21.25–26.25 10% >26.25 Controls **25(OH)D:** 26% <20 74% >20 **Calcium**: 7% <21.25 78% 21.25–2.63 15% >26.25	Calcium intakes not reported March 2004 to February 2005
37	Prentice et al (2008) MRC Keneba and MRC Fajara in The Gambia. Immunoradiometric assay	Analysis of stored samples from 46 children who had presented with rickets-like bone deformities. (65% male) Age range: 1.1-16.4 years Geometric mean (-1SD, +1SD) = 3.4 (1.9, 6.4) y 13 patients with active rickets. 33 patients with non-active rickets. 147 children from an earlier research study used as reference data.	Radiographs reviewed and assessed by Thacher et al method (Annex 1) Patients classified as having active rickets (bone deformities plus biochemical indicators) or non-active rickets (bone deformities only).	**Active rickets** (n=13): 25(OH)D: 42.4 (28.6, 56.1) Ca: 91.2 (84, 98.4) **Non-active rickets** (n=33) 25(OH)D: 50.7 (37.9,63.4) Ca: 95.2 (89.6, 100.4) **Reference children** (n=147) 25(OH)D: 95.0 (75.3, 114.6) Ca: 92 (84.4, 99.6)	Calcium intakes Majority prescribed calcium lactate pentahydrate (300 mg providing 39 mg elemental Ca) in the 6-12 months before follow-up. Median doses over 6 months Ca: 117 mg/d D2: 250 µg (10,000 IU)/d)
38	Ozkan et al (2009) Erzurum, Turkey RIA (IDS)	39,000 children attending paediatric outpatient clinic. Age: 0-3 years Confirmed rickets cases compared to controls. Control group chosen from 'age-matched children with normal vitamin D levels'. (Vitamin D deficiency defined as 25(OH)D <25nmol/L.) During 1 year, 39 cases (0.1%) diagnosed with rickets	Rickets cases identified through clinical sign & confirmed through radiological & laboratory findings. Clinical rickets diagnosed in children with 2 or more of following criteria: craniotabes, rachitic rosary, bilateral widened wrists, frontal bossing, bowing legs, fractures, tetany, convulsion and Harrison's sulcus.	Cases/controls, 25(OH)D (mean): 5.8/17.9 Ca: 75/95 Maternal 25(OH)D (cases/controls): 14.9/19.4	Calcium intakes not reported Study examined incidence of rickets among children in Eastern Turkey.

Table 5 - Intervention/Dose response/RCT

ID	Author/year/location/25OHD measurement method	Population	Rickets diagnosis	Treatment	Mean 25(OH)D (nmol/L) & Ca (mg/L) concentrations	Calcium intakes/other comments
39	Cesur et al (2003) Van, Turkey RIA	56 patients with nutritional VDDR (52 for follow-up). 36 males (64%) Mean age 10.7 (6.1) months 20 age-matched controls. Mean age 11.7 (8.0) months	Based on history, clinical and laboratory findings.	Participants randomly assigned to vitamin D (single dose): Gp 1 (n=20): 3750 µg (150,000 IU) Gp 2 (n=20): 7500 µg (300,000 IU) Gp 3 (n=16): 15000 µg (600,000 IU)	Before treatment**:** 25(OH)D3 Stage 1: 15.8 (6.4) Stage 2: 15.4 (4.8) Stage 3: 14.7 (3.9) Patient group Ca: **Before:** 78.2 (13.5) Control group Ca: **Before:** 89.0 (4.6)	Calcium intakes not reported. Stage 1 rickets: serum Ca low but P normal Stage 2: serum Ca normal due to compensatory hyperparathyroidism Stage 3: both serum Ca & P low No useful info on after treatment.
40	Rajah et al (2010) Abu Dhabi, UAE UV detection using Chromsystems kits	Retrospective audit of 10 children with nutritional rickets. Age: 21.20 (8.41) m 90% Arab ethnicity; 60% male.	Inclusion criteria - patients who met definition of rickets (radiologically & biochemically) and on current therapy with alphacalcidol.	7 patients treated with 50µg/d (2000 IU) of D2 drops for 3 months and subsequently 10 µg (400 IU)/d. 3 patients treated with stoss therapy of 15,000 µg (600,000 IU) intramuscular as a single dose.	**25(OH)D** Baseline: Total: 37.70 (25.85) Drops: 35/Stoss: 40 1 month 25(OH)D (*estimates from box plots)* Drops: 48/Stoss: 90 2 months 25(OH)D (*estimates from box plots)* Drops: 105/Stoss: 225 **Ca** Baseline: Drops: 92 (4)/Stoss: 89.8 (3.68) 1 month: Drops: 94.9 (5.71)/Stoss: 90.6 (1.98) 2 months: Drops: 94.6 (2.18)/Stoss: 95.08 (3.67)	Calcium intakes not reported. Rapid healing (within 3 months) followed introduction of therapeutic doses of D2 (either oral or stoss therapy).
41	Emel et al 2012 Bezmialem, Turkey Electrochemiluminescense enzyme immunassay method (ECLIA) (ADVIA Centaur)	42 patients: Age: 5 months to 3 years • 26 boys, 16 girls • 25(OH)D <50 nmol/L 6 patients with 25(OH)D <25 nmol/L and "serious clinical presentations of rickets (such as bone deformities; 1 patient admitted with hypocalcaemic seizures)."	Clinical features of all patients: enlarged wrist & ankles (95%), failure to thrive (76%), muscle weakness (52%), bowing of tibia & femur (42%), frontal bossing (28%), delayed fontanel closure (14%), leg pain (14%), rachitic rosary (11%), Harrison grove (11%), seizures (2%).	Group 1: 50 µg/d D3 for 6 weeks Group 2: 3,750 µg single dose D3 Both groups received calcium lactate (50mg/kg/day) for first two weeks of intervention.	**25(OH)D** Baseline Group 1: 14.4 Group 2: 13.7 Post-intervention Group 1: 25.4 Group 2: 50.4 **Calcium** Baseline Group 1: 99 group 2: 92 Post-intervention calcium: Group 1: 101 Group 2: 99	Calcium intakes: All received calcium lactate (50mg/kg/d) for 2 weeks.

Osteomalacia

Table 6: Case reports

Author/yr/location/25OHD measurement method	**Population**	**Osteomalacia diagnosis**	**Mean serum 25(OH)D (nmol/L) & Ca (mmol/L) concentrations**
Clark et al (1972) Newcastle upon Tyne, UK Method not reported	Patients: n = 15 (7 male, 8 female), age 11-42 y, South Asian ethnic origin, living in the UK ≥ 1 yr (mean 4.5 y) Presented with spontaneous pain, usually in the legs, 4 seen following minor injury Blood relatives: n = 18, age 8-48 y 3 had symptoms of limb pain	Biochemical evidence of rickets and osteomalacia 12/15 patients and 2/18 relatives had radiological evidence 2/3 patients histological evidence	**25(OH)D: not reported** Patients: Ca: 2.1 Blood relatives: Ca: 2.3
Moncrieff & Fadahunsi (1974) Derby, UK Method not reported	Female (pregnant) - age 30 y, South Asian ethnic origin Presented with pain in sacrum and waddling gait during latter part of pregnancy Infant - female, born at term by spontaneous delivery	Biochemical and clinical evidence of osteomalacia ; x-ray of pelvis did not show osteomalacia Infant - clinical, biochemical (low serum calcium and raised alkaline phosphatase) and radiological features of rickets	*After delivery:* **25(OH)D: 17.8** Ca: 2.1 Infant - **25(OH)D: 20.8** *At 4 days old* -Ca: 1.7
Russell and Hill (1974) Manchester, UK Method not reported	Female (pregnant) - age 30 y South Asian ethnic origin Presented with signs of pre-eclampsia at 37 weeks gestation (not treated) Infant - male, delivered spontaneously	*37 weeks gestation*: no clinical evidence of osteomalacia, x-ray confirmed fetal rickets *4 months after delivery*: biochemical evidence of osteomalacia, x-ray normal Infant - x-ray of wrists confirmed rickets, no clinical abnormalities	*At 37 weeks gestation*: **25(OH)D : 7.5** Ca: 1.8 *4 months after delivery:* **25(OH)D: 6.75** Ca: 1.9
De la Jara et al (2004) Switzerland Radioimmunoassay and an iodine-125 labelled tracer	11 female asylum seekers with symptomatic hypovitaminosis D_3 From Bosnia, Afghanistan, Somalia, Albania, Ethiopia Presented with minimal exposure to sunlight and a history of bone pain, proximal muscular weakness, change in gait, or fatigue.	25(OH)D level 25(OH)D < 20 nmol/L considered sever deficiency	At diagnosis - **25(OH)D: 10.9 (3.8)** range 4.5-16.2; 64% < 12 Ca: n=10 patients: 2.19 (0.09) n=4: hypocalcaemia (<2.15 mmol/L)
Cardinal and Gregory (2009) Cambridge, UK Radioimmunoassay	Female, age 75 y, White Schizophrenic, inpatient in psychiatric hospital for more than 35 years; investigated due to persistent elevated alkaline phosphatase & intermittently low phosphate and calcium concentrations	Case report - biochemical evidence of osteomalacia	**25(OH)D: 10.5**

Author/yr/location/25OHD measurement method	**Population**	**Osteomalacia diagnosis**	**Mean serum 25(OH)D (nmol/L) & Ca (mmol/L) concentrations**
Brouwers et al (2010) Netherlands Method not reported	2 brothers South Asian ethnic origin, living in Netherlands (2 years) Patient 1 - age 12 y Presented with waddling gait, muscular weakness and bone pain Patient 2 -age 14y Presented with waddling gait and pain when climbing stairs	Biochemical, clinical and radiographic evidence of rickets	Patient 1 - **25(OH)D: 8** Ca: 1.9 Patient 2 - **25(OH)D: 4** Ca: not reported
Thabit et al (2011) Ireland Radioimmunoassay	Case 1 male, age 31 y , South Asian ethnic origin, living in Ireland (5 years) Case 2 Female, age 34 y, South Asian ethnic origin, living in Ireland (9 years)	Case 1 - 2 day history of upper and lower limb tetany; unable to stand unaided due to progression of bilateral lower limb weakness and biochemical evidence of osteomalacia Case 2 - pains pelvic region for 4 years; complained of proximal muscle weakness and difficulty walking, significant proximal myopathy and waddling gait and biochemical evidence of osteomalacia	Case 1 - **25(OH)D: 5.5** Ca: 1.43 Case 2 - **25(OH)D: 16** Ca: 2.04
Mittal et al (2012) India Method not reported	Male age 41y Presented with gradually progressive quadriparesis for past 6 months	Based on symptoms; Confirmed by dramtic improvements with vitamin D supplements	**25(OH)D:** 20.3 Ca: 2.03
Zurlo and Wagner (2012) Livingstone, US Method not reported	Male, age 8 months African American; almost exclusively breast fed Presented at A&E with fever	X-rays showed flaring of the ribs at the costochondral junction and fraying and cupping of the distal radial and ulnar metaphyses and biochemical evidence of rickets	**25(OH)D: below detection (<12.0)** Ca: normal (concentration not reported)

Table 7: Observational studies

Author/yr/location/25OHD measurement method	**Population**	**Osteomalacia diagnosis**	**Mean 25(OH)D (nmol/L) & Ca (mmol/L) concentrations**
Preece et al (1975) Glasgow, Scotland	35 patients (age not reported) South Asian ethnic origin with overt rickets or osteomalacia	Clinical and biochemical evidence and, in the majority, radiological confirmation.	Hypocalcaemic (n=22) (Ca: <2.2) **25(OH)D: 7.5** Others (n=21) (Ca not reported) **25(OH)D: undetectable**
Gifre et al (2011) Barcelona, Spain Radioimmunoassay	28 adults (12 male, 16 female), mean age 55±28 y (range 17-87 y) 26 white; 2 of south Asian ethnic origin 14/28 hypo-phosphatasia osteomalacia 13/28 vitamin D osteomalacia	Bone biopsy and/or by the Bingham & Fitzpatrick criteria defined as two of the following: low Ca, low P, elevated total AP, suggestive radiographs	Whole group: **25(OH)D: 40 (37)** Ca: 2.2±0.3 Vitamin D osteomalacia patients: **25(OH)D: 15 (5)** (100% 25(OH)D < 30 nmol/L) Ca: 1.98 ± 0.33 Hypo-phosphatasia group: **25(OH)D: 62 (42)** (14% 25(OH)D < 30 nmol/L) Ca: 2.25 ± 0.18
Torun et al (2013) Istanbul, Turkey Electrochemiluminescense enzyme immunoassay method	543 patients, age 1-17 y referred to hospital with symptoms of vitamin D deficiency	Diagnosed according to 25(OH)D concentrations as: Vitamin D deficient(<25 nmol/L) or Vitamin D insufficient (25- 50 nmol/L)	**25(OH)D:** 1-3 y: 32 (11) 4-6 y: 28 (11) 7-11 y :23 (11) 12-17 y: 20 (11.5)

Pregnancy and lactation

Table 8: Cohort studies investigating maternal vitamin D concentrations and effects on bone health measures in offspring

Author/Year	Population	Design	25(OH)D Maternal (nmol/L)	25(OH)D Cord (nmol/L)	Comments
Mahon (2010) Southampton, UK	Pregnant young women (n=424) Age: 20-34 years	Longitudinal	5.9% below 25nmol/L 30.7% below 50nmol/L	Not measured	25(OH)D status in mothers below 25nmol/L and between 25-50nmol/L had increased femoral splaying indices compared with above 50nmol/L.
Prentice (2009) The Gambia, Africa	Pregnant women (n=125) and their infants	Original Ca RCT. Cross-sectional with longitudinal follow up	20 weeks pregnancy: 103nmol/L 36 weeks pregnancy 111nmol/L	Not measured	No relationship between maternal 25(OH)D concentrations and indices of bone health in the infants
Vijakainen (2010) Helsinki, Finland	Pregnant women (n=125) Age: 20-40 years	Cross-sectional and longitudinal	41.0nmol/L during 1st trimester	50.7 nmol/L	Used cut off 42.6nmol/L. Infants born to mother above median cut-off had 13% higher tibia BMC
Young (2012) Baltimore, USA	171 Pregnant adolescent girls (n=171) and their infants Age: <18 yrs	Longitudinal follow up	26 weeks gestation and at delivery: 54.7 [27.5] nmol/L	Not measured	Maternal 25(OH)D concentration at 26 weeks and delivery was positively associated with femur and humerus z scores.
Dror (2012) California, USA	Mother-infant pairs (n=80)	Cross-sectional with longitudinal follow up	Maternal and cord 25(OH)D : African American: 69.1 [26.1] nmol/L Non-African American: 82.3 [30.3] nmol/L	African American: 36.0 [31.7] nmol/L Non-African American: 48.2 [41.4] nmol/L	Cord serum BSAP concentration was inversely correlated with infant whole body BMC and with cord serum 25(OH)D concentration but there was no association between cord serum 25(OH)D concentration and whole body BMC.

Table 9: RCTs: Vitamin D supplementation and bone health indices in infants aged 0-12 months of age

Author/ Year	Population	Intervention & duration	25(OH)D status (nmol/L)	Bone health results	Comments
Kim (2010) Cheongiu, Korea	New born infants (n=74)	10µg (400IU) per day vitamin D in breast-fed infants 12 months	Not fully presented	Higher 25(OH)D, lower PTH. No difference in BMD	Poor study design. Number of core uncertainties.
Kumar (2011) New Delhi, India	Low birth-weight infants (n=2079)	35µg (1400IU) per week vitamin D 6 months	After 6 months supplementation: Vitamin D: 55 [22.5] Control: 36 [25.5]	Vit D supplement increased SD z scores at 6 months for Wt, length and arm circumference	Key study for low birth weight infants Subject numbers smaller than highlighted in abstract (n=216 in vit D group; n=237 in placebo group
Abrams (2012) Houston, USA	Infants aged 1 week (n=38)	10µg/400 IU per day 3 months	Not measured	25(OH)D status: Non-Hispanic - 57nmol/L (23ng/ml) Hispanic: 42nmol/L (16.9 ng/ml) No relationship with bone health indices	Low subject numbers Limited time allowed to see a difference in bone indices Important study re effectiveness of 10µg/400IU per day on raising 25(OH)D concentrations
Holmlund-Suila et al 2012 Finland	Infants aged 2 weeks (n=113)	1.10µg/d (400IU) 2. 30µg/d (1200IU) 3.40µg/d (1600IU) 10 weeks	1. 88nmol/l 2. 124nmol/l 3. 153nmol/l	No difference in PTH or bone turnover markers. Using peripheral quantitative computed tomography – in a multivariate ANCOVA there was a trend toward better stress and strain index and larger total bone and cortical bone area was noted with higher vitamin D doses.	10 weeks is a short treatment time to show change in bone architecture and mineral accrual

Children and adolescents

Table 10 - Systematic reviews of bone health indices

Author	Methods	Results	Conclusions
Winzenberg et al (2011) Vitamin D supplementation for improving bone mineral density in children	**Selection criteria:** *Inclusion:* Randomised controlled trials of vitamin D supplementation compared with placebo, with a treatment period of at least three months. Trials in children and adolescents (aged < 20 years) without coexistent medical conditions or treatments causing osteoporosis. Trials of vitamin D supplementation regardless of regardless of type or dose of vitamin D supplement or method of administration, compared with placebo. *Exclusion:* Studies performed exclusively in neonates (aged < 1 month trials with a treatment period of less than three months. Outcome measure Bone mineral density	6 RCTs (n=884; vit D3 133IU/d to 1400IU/wk; mean serum 17.7-49.5nmol/l) Total body BMC (5 RCTs) SMD 0.10 (95%CI -0.06, 0.26) (p=0.21) Hip BMD (4 RCTs) SMD 0.06 (95%CI -0.18, 0.29) (p=0.64) Forearm BMD (3 studies) SMD 0.04 (95%CI -0.36, 0.45) (p=0.84) Lumbar spine BMD (5 studies) SMD 0.15 (95%CI -0.01, 0.31) (p=0.07) *Comparison by baseline 25(OH)D* Total body BMC >35nmol/l (2 RCTs) SMD -0.07 (95%CI 0.33, 0.18) (p=0.57) <35nmol/l (3 RCTs) SMD 0.21 (95%CI 0.01, 0.41) (p=0.04) Hip BMD >35nmol/l (3 RCTs) SMD -0.02 (95%CI -0.31, 0.28) (p=0.91) <35nmol/l (1 RCT) SMD 0.25 (95%CI -0.07, 0.58) (p=0.12) Lumbar spine >35nmol/l (3 RCTs) SMD 0.09 (95%CI -0.10, 0.28) (p=0.35) <35nmol/l (2 RCTs) SMD 0.31 (95%CI 0, 0.61) (p=0.048) Forearm >35nmol/l (2 RCTs) SMD 0.12 (95%CI -0.62, 0.85) (p=0.76) <35nmol/l (1 RCT) SMD -0.06 (95%CI -0.38, 0.26) (p=0.71)	Vitamin D supplementation had no statistically significant effects on total body BMC, hip bone BMD or forearm BMD. There was a small significant effect on lumbar spine BMD. There was a significant effect on total BMC and lumbar spine BMD in studies reported baseline serum 25(OH)D concentrations <35nmol/l.

Table 11: RCTs of Vitamin D supplementation on bone health indices in children and adolescents

Author/Year	Population	Intervention/ duration	Baseline 25(OH)D concentration (nmol/L)	Post intervention 25(OH)D concentration (nmol/L)	Effects on bone health indices
Park (2010) Purdue, USA	Females (n=11); aged 12-14y	25ug/d (1000IU) vitamin D3; 4 weeks	Mean increase in serum 25(OH)D concentration of 13.3	Mean increase in serum 25(OH)D concentration of 13.3	No improvement in fractional Ca absorption, net Ca absorption or Ca retention
Molgaard (2010) Copenhagen & Frederiksbar, Denmark	Females (n=221) aged 11-12y	1. 5ug/d (200IU) vitamin D3 2. 10ug/d (400IU) vitamin D3 12 months	1.41.9 2.44.4	1. 52.9 2. 57.9	No effect of either 5 or 10 µg/d supplement on bone markers of turnover or whole body/lumbar spine bone mineral augmentation FF VDR genotype vitamin D supplementation increased whole bone BMD and BMC
Ghazi (2010) Tehran, Iran	Males (n=105) & females (n=105) aged 14-20y	1. 1250 µg (50000IU) monthly (40µg/d 1600IU/d) 2. 1250µg (50000IU) bi-monthly (20µg/d 800IU/d) 3. placebo; 6 months	1. 32 [±22] 2.28.2 (±24)	1. 60 (±27.5) 2. 45.7 (±24)	No change in urinary CTX. Significant increase in osteocalcin in both vitamin D groups. Significant decrease in PTH
Khadilkar et al (2010) India	Girls (n=50) Mean age 14.6y (14.3-15.3y)	1. 7500µg (300000IU) 4 times a year plus 250mg/d calcium 2. Placebo/ 4 times a year plus 250mg/d calcium Duration: 1 year	1.24.5nmol/l (12.7-33.2) 2.20.8nmol/l (12.7-30.4)	1. 75.2nmol/l (64.2-85.5) 2. 28.1nmol/l (16.7-34.0)	No significant difference in bone outcome measure in the two groups. However, there was a positive effect of intervention in the size adjusted total body bone area ($p<0.05$), total body bone mineral content ($p<0.05$) and lumbar spine bone mineral content ($p<0.05$), and positive trend in lumbar spine bone area ($p=0.07$) in girls who were within 2 years of menarche. Pilot study.
Ward et al (2010) Manchester, UK	Postmenarchal girls 12-14 years (n=69) 88% South Asian	1. 3750µg (150,000 IU) 4 times a year 2. Placebo 4 times a year Duration: 1 year	1.18.1nmol/l (8.0) 2.17.9nmol/l (7.4)	1. 56.0 nmol/l (8.9) 2. 15.7nmol/l (6.6)	The effects of vitamin D treatment were small and non significant.

Younger and adult population groups

Table 12: RCTs of Vitamin D supplementation on bone health indices in adults

Author/Year	Location	Population	Intervention/ duration	Baseline 25(OH)D concentration (nmol/L)	Post intervention 25(OH)D concentration (nmol/L)	Effects on bone health indices
Islam et al (2010)	Bangladesh	Pre-menopausal women 18-36 years (n=200)	1.10µg/d (400IU) 2.10µg/d (400IU) & 600mg calcium 3.10µg/d (400IU) & 600mg calcium & multiple mineral supplement 4.Placebo Duration: 1 year	1. 37.1nmol (12.1) 2. 37.8nmol/l (10.9) 3. 36.9nmol/l (12.5) 4. 35nmol/l (9.4)	Increase by: 1. 32.2nmol/l (23.7) 2. 32.4nmol/l (24.3) 3. 28.8nmol/l (24.8) 4. 0.6nmol/l (13.8)	There was increased BMD and BMC at the femoral neck in vitamin D groups compared to placebo. Bone mineral augmentation also increased significantly at the femur at the end of the intervention. There was a positive effect of supplementation on BMD and BMC of the greater trochanter and Ward's triangle compared with the placebo group. There was no significant difference in BMD and BMC of the lumbar spine. .

Muscle strength in younger adults and adults

Table 13 Meta-analyses

Study	Methods	Results	Conclusions
Tomlinson et al 2014 Effects of vitamin D supplementation on upper and lower body muscle strength levels in healthy individuals. A systematic review with meta-analysis	Selection criteria *Inclusion:* Studies were included if they were published in English, employed a control group, and measured muscle strength as one of their primary outcome measures. Studies were required to supplement participants with vitamin D only in at least one arm of their study. *Exclusion:* Aged <18 years, non healthy subjects. Outcome measure Upper and low limb muscle strength	6 RCTs, 1 controlled trial; n=310 adults; mean age 21.5-31.5 years; 67% female Vit D supplement doses range from 100µg/d to 1500µg/weekly Upper limb strength 0.32 (95%CI 0.10, 0.54) Lower limb strength 0.32 (95%CI 0.01, 0.63)	Significant increase in upper and lower limb muscle strength with vitamin D supplementation.

Younger adults and adult - fractures

Table 14 Meta-analyses

Study	Methods	Results	Conclusions
Dao et al (2014) Serum 25Hydroxyvitamin D levels and stress fractures in military personnel: a systematic review and meta-analysis	Selection criteria: *Inclusion:* Any type of studies examining the association between stress fractures and serum 25(OH)D levels; participants aged ≥18 years; participants involved in any branch of a country's military force (i.e. army, navy, air force, marine corps); and studies published in the English. *Exclusion:* Case reports and series (<10 participants); review articles; guidelines; basic science and animal studies; conference abstracts; and athletes. Outcome measure Stress fractures	8 studies (2634 military personnel, 18-30y, 44% male) 25(OH)D measured at time of diagnosis (3 studies) -2.26 (95%CI -3.89, -0.63) ((p=0.007) 25(OH)D measured at entry to basic training (5 studies) -2.63 (95%CI -5.80, 0.54) (p=0.10)	Mean 25(OH)D was lower in cases of stress fracture at time of entry into basic training and at time of stress fracture diagnosis.

Table 15: RCTs of Vitamin D supplementation on fracture reduction

Author/Year/country	Population	Intervention & duration	Baseline 25(OH)D status Calcium intake	Post intervention 25(OH)D status	Results	Comments
Lappe et al 2008	Female Navy recruits Median age 19 years (17-35 years) (n=5201)	1. 200µg (8000IU) vitamin D & 2000mg calcium 2. Placebo Duration: 8 weeks	Not reported	Not reported	309 subjects with stress fractures. Supplemented group had 20% lower incidence of stress fracture than control 5.3% vs 6.6% (p<0.0026) RR 0.80 (95%CI 0.64, 0.99). Per protocol analysis there were 21% fewer fractures in supplemented gp vs control gp (6.8% vs 8.6%).	There was a lower risk of fracture in the supplemented group. No 25(OH)D levels were reported.

Postmenopausal women and older adults

Bone health indices

Table 16- Meta-analyses

Study	Methods	Results	Conclusions
Reid et al (2014) Effects of vitamin D supplements on bone mineral density: a systematic review and meta-analysis	Selection criteria: *Inclusion*: RCTs comparing interventions that differed only in vitamin d content; adults >20 years; intervention with vitamin D2 and D3. If other intervention given (e.g. calcium) they had to be the same in all groups. *Exclusion*: vitamin D metabolite, individuals with other disorders likely to affect bone and calcium metabolism. Outcome measure Bone mineral density	23 trials (n=4082, mean age 59 years, mean duration 23.5 months, 92% women) Mean 25(OH)D concentration was less than 30nmol/L in 5 trials, 30–50nmol/L in 3 studies, 50–75nmol/L in 11 studies, and more than 75nmol/L in 1 study. Calcium supplements were given in 12 trials. Lumbar spine (17 RCTs) RR 0.0 (95%CI -0.2, 0.3) p=0.8 Femoral neck (13 RCTs) RR 0.8 (95%CI 0.2, 1.4) (p=0.005) Hip/trochanter (15 RCTs) RR 0.2 (95%CI 0.1, 0.4) (p=0.17) Total body (8 RCTs) RR -0.3 (95%CI 0.7, 0.1) (p=0.2) Forearm (6 RCTs) RR -0.3 (95%CI -0.7, 0.1) (p=0.09)	There was a small benefit at the femoral neck, but no effect at any other site.

Table 17 - RCTs of vitamin D supplementation on bone mineral density in postmenopausal women and elderly women and men

Author/Year	Location	Population	Intervention	Baseline 25(OH)D conc (nmol/L)	Post intervention 25(OH)D conc (nmol/L)	Effects on Bone Health Indices
Karkkaiinen (2010)	Finland - Kuopio	Postmenopausal women (n=593) Aged 65-71 years. Healthy population	1. 20µg (800IU)/d vitamin D and 1000mg Ca 2. Placebo 3 year supplementation	1. 50.1nmo/l (±18.8) 2. 49.2nmol/l (±17.7)	1. 74.6nmol/l (±21.9) 2. 55.9nmol/l (±21.8)	Significant increase in BMD at the total body in the supplementation group using ITT analysis. Compliers analysis increased significance with the femur sites being significant.
Macdonald et al 2013	Scotland UK	Healthy postmenopausal women 60-70 years Mean age 64.6 (2.3) (n=305)	1. 10µg (400 IU) 2. 25µg (1000 IU) 3. Placebo Duration: 1 year	1. 33.4 ±13.2nmol/l 2. 33.2 ±13.8nmol/l 3. 35.8 ±16.4nmol/l	1. 65.0 ±19.7nmol/l 2. 75.9 ±18.9nmol/l 3. 32.0 ±14.9nmol/l	Mean BMD loss at the hip was significantly less for the 1000 IU vitamin D group (0.05%1.46%) compared with the 400 IU vitamin D or placebo groups. There was no significant difference in changes in BMD at the lumbar spine in the groups. Treatment did not change markers of bone metabolism, except for a small reduction in PTH and an increase in serum calcium (latter with 1000 IU dose only).

Table 18 Cohort studies of 25(OH)D concentration and BMD/bone turnover in postmenopausal women and elderly men and women

Reference/ country	Population description	Follow up	Mean 25(OH)D	Results	Comments
Ensrud et al. (2009)	Community dwelling men Age: 65 years plus (n=1279)	4.4 years	59nmol/L (23.8ng/ml) (median 63.4nmol/L (51-75) 9% <37nmol/l (15ng/ml) 14% 37-50nmol/l (15-19.9ng/m)l 47% 50-75nmol/l (20-29.9ng/ml) 29% >75 (30ng/ml)	Lower 25(OH)D levels were associated with higher rates of bone loss at total hip p=0.01. Men with 25(OH)D levels <75nmol/L (19.1ng/ml) experienced 1.5 fold higher rate of hip bone loss p=0.003 and for trochanter p=0.05 for quitnitle 1 vs quintile 2-5.	Hip bone loss was greater in men with 25(OH)D levels < 49.9nmol/l, particularly in those aged ≥75y.

Table 19 Meta-analyses (+/- calcium) ***with further information on mean baseline 25(OH)D concentrations in the included studies***

Study	Methods	Results	Conclusions
Avenell et al (2014) Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men	Selection criteria: *Inclusion:* randomised or quasi-randomised trials that compared vitamin D related compounds, alone or with carlcium, against placebo, no intervention or calcium alone and that reported fracture outcomes in older people. *Exclusion:* interventions that included treatments other than vitamin D or calcium. Studies in which participants were on corticosteroid therapy. Outcome measure Primary outcome: hip fracture. Secondary outcomes: any non-vertebral fracture, vertebral fracture, any new fracture, adverse effects.	53 trials (n=9791): 31 trials examined vitamin D with or without calcium in prevention of fractures in the community, nursing home or hospital inpatient population; 22 trials examined calcitrol or alfacalcidol, mostly with participants who had established osteoporosis. ***Vitamin D alone vs placebo or no treatment*** Hip fracture (11 trials, n=27,693): RR 1.12 (95%CI 0.98, 1.29) Non-vertebral fractures (12 trials, n=22,930): RR 1.05 (95%CI 0.96, 1.14) Vertebral fractures (6 trials, n=11,396): RR 1.03 (95%CI 0.76, 1.39) Any new fracture (15 trials, n=28,271): RR 1.03 (95%CI 0.96, 1.11) ***Vitamin D plus calcium vs calcium alone*** Hip fracture (7 trials, n=7411): RR 0.84 (95%CI 0.63, 1.13) Non-vertebral fractures (6 trials, n=3336): RR 0.96 (95%CI 0.76, 1.16) Vertebral fracture (2 trials, n=2681): RR 0.14 (95%CI 0.01, 2.77) ***Vitamin D plus calcium vs placebo or no treatment*** Hip fracture (9 trials, n= 49,853): RR 0.84 (95%CI 0.74, 0.96) Non-vertebral fractures (8 trials, n=10,380): RR 0.86 (95%CI 0.78, 0.96) Vertebral fractures (4 trials, n=42,185): RR 0.89 (95%CI 0.74, 1.09) Any fracture (10 trials, n=49,976); RR 0.95 (95%CI 0.9, 0.99)	Vitamin D alone had no effect on preventing hip fracture, non-vertebral fracture, vertebral fractures or any new fractures. Vitamin D with calcium supplements may prevent hip or any type of fracture.
Bolland et al 2014 The effect if vitamin D supplementation on skeletal, vascular, or cancer outcomes: a trial sequential meta-analysis	Selection criteria: *Inclusion:* RCTs included in meta-analyses studying vitamin D with the outcome fracture. *Exclusion:* cluster randomised trials, trials of hydroxylated vitamin D or vitamin D analogues, trials that included other interventions only in the vitamin D group, trials of fortified dairy products, and trials in populations with chronic comorbidity other than osteoporosis or frailty Outcome measure Fractures	*Total fracture (22 RCTs; 76431 participants)* Vitamin D only RR 0.97 (95%CI 0.88, 1.08) Vitamin D and calcium RR 0.92 (95%CI 0.85, 0.99) Vitamin D with and without calcium RR 0.95 (95%CI 0.88, 1.02) p=0.13 *Hip fracture* Vitamin D only RR 1.11 (95%CI 0.97, 1.27) Vitamin D and calcium RR 0.84 (95%CI 0.74, 0.96) Vitamin D with and without calcium RR 0.97 (95%CI 0.86, 1.08) p=0.55	The results of the trial sequential meta-analysis found that vitamin D supplementation with or without calcium does not reduce skeletal outcomes in community dwelling individuals more than 15%.

Study	Methods	Results	Conclusions
Bischoff-Ferrari et al., 2009 Prevention of nonvertebral fractures with oral vitamin D and dose dependency	Selection criteria *Inclusion:* Oral vitamin D supplementation (D2 or D3); minimum follow-up, 1 year; more than 1 fracture; mean age of study subjects ≥65 y; double-blinded study design; report of adherence; explanation of how fractures ascertained. *Exclusion*: Uncontrolled trials; observational studies, animal studies; studies with patients following organ transplantation or stroke, receiving steroid therapy or care for Parkinson's disease or having unstable health states. Outcome measure First or repeated nonvertebral fracture or hip fracture in persons receiving supplemental vitamin D with or without calcium supplementation compared with those receiving placebo or calcium supplementation alone. Effect of dose - calculated received dose of supplemental vitamin D by cross-product of dose & percentage adherence.	12 double-blind RCTs; n=42,279; 89% women Nonvertebral fractures (12 RCTs) RR = 0.86 (0.77-0.96); heterogeneity seen (Q test: p=0.04). Heterogeneity resolved after stratifying trials by received dose For 3 trials ≤ 10 µg (400 IU), RR = 1.02 (0.92-1.15) (Q test, p=0.64) For 9 trials ≥ 10 µg (400 IU), RR = 0.80 (0.72-0.89) (Q test, p=0.31) Hip fractures (8 RCTs) RR = 0.91 (0.78-1.05); heterogeneity seen (Q test, p=0.08) Heterogeneity resolved after stratifying trials by received dose For 3 trials ≤ 10 µg (400 IU), RR = 1.09 (0.90-1.32) (Q test, p=0.81) For 5 trials ≥ 10 µg (400 IU), RR = 0.82 (0.69-0.97) (Q test, p=0.18)	A higher received dose of supplemental vitamin D (12-19 µg/482-770 IU daily) should reduce nonvertebral fractures by at least 20% and hip fractures by at least 18%.

Table 20: RCTs of vitamin D supplementation on fracture reduction in postmenopausal women and older women and men

Author/Year/ country	Population	Intervention & duration	Baseline 25(OH)D status Calcium intake	Post intervention 25(OH)D status	Results	Comments
Sanders (2012) Australia - Victoria	Women (n=2256) aged 70 years and over. Women considered to be at high risk of fracture	1. 12,500 µg (500,000 IU) of vitamin D3 given a single annual dose orally 2. Placebo Duration: 3-5 years	Median (IQR) All: 49nmol/l (40-63) (n=131) 1. 53nmol/l (40-65) (n=74) 2. 45nmol/l (40-57) (n=57)	12m post-dose: 74 nmol/L or higher 1. 9.5% 2. 5.3% 51-74nmol/L 1. 44.5% 2.33.32% 26-50 nmol/L 1. 41.9% 2. 57.9% 25nmol/L or less: 1. 4% 2. 3.5%	No. of fractures 1.171 2. 135 RR 1.26 (95%CI 1.00-1.59) (p=0.047) Vitamin D vs placebo group	There was a significant increase in fracture in the vitamin D group compared to the placebo group.

Table 21 Prospective studies on association between 25(OH)D concentration and fracture risk in older men & women

Reference/ Country	Population Description	Follow-up	Mean 25(OH)D (nmol/L) (± SD) baseline	Results	Comments
Nakamura et al (2011) Japan	Community-dwelling women Aged 69 years and older (n=773)	6 years	60nmol/l (± 17.6)	No. of fractures 50/4250 (person years) Q1 (≤47.7) 15.4 /1000 person years Q2 (≥47.7 - <59.2) 11.5 /1000 person years Q3 (≥59.2 -< 71.0) 14.9 /1000 person years Q4 (≥71.0) 5.5 /1000 person years Q1 vs Q4 2.82 (95%CI 1.09, 7.34) Q2 vs Q4 1.84 (95%CI 0.68, 4.98) Q3 vs Q4 2.82 (95%CI 1.09, 7.27)	Women in the highest quartile of serum 25(OH)D concentration had a lower risk of fracture.
Rouzi et al (2012) Saudi Arabia	Healthy postmenopausal women (n=912) mean age, 61.3 ± 7.2 years	5.2 ± 1.3 years	All subjects 34.27nmol/l ± 22.80 Without fracture 35.16nmol/l ±23.28 With fracture 30.91±20.59	Q1 vs Q2 (<17.9 vs >45.1nmol/l) RR 1.63 (95%CI 1.06-2.51)	The lowest quartile of serum 25(OH)D was an independent risk factor for osteoporosis related fractures.
Barbour et al (2012)	Community dwelling white and black subjects from Health ABC study. (n=2614) Age >70 years	Hip fractures 6.4 years (6.1-6.5) Non spine fractures 6.4 years (5.5-6.5)	Hip fracture (median (IQR)) 26.3 (15.9-31.9) No hip fracture (median (IQR)) 24.3 (17.8-31.9) Non spine fracture (median (IQR)) 24.7 (16.5-32.2) No non spine fracture (median (IQR)) 24.3 (17.9-31.8)	84 hip fractures 247 non spine fractures The multivariable adjusted HRs (95% CIs) of hip fracture for participants in the lowest (≤17.78ng/ml), second (17.79-24.36 ng/ml) and third quartile (24.37-31.94 ng/ml) of 25(OH)D were 1.92 (0.97-3.83), 0.75 (0.32-1.72) and 1.86 (1.00-3.45), respectively; compared with participants in the highest 25(OH)D quartile (>31.94ng/ml) (p-trend=0.217)	There is limited evidence to support an association between 25(OH)D and hip fracture and no evidence of an association with non spine fractures.

Table 22 - Meta-analyses

Study	Methods	Results	Conclusions
Muir et al (2011) Effect of vitamin D supplementation on muscle strength, gait and balance in older adults: a systematic review and meta-analysis	Selection criteria: *Inclusion*: Randomised controlled trial of supplemental vitamin D or associated metabolite, with or without calcium, with a placebo or standard treatment arm; older adults aged 60years plus; physical performance measures of muscle strength, gait or balance measured at baseline and at the end of the study. *Exclusion*: Study did not include an exercise intervention Outcome measure The effect of vitamin D supplements in older adults on muscle strength, gait and balance without an exercise intervention.	13 RCTs; mean age 78y ***Postural sway*** (3 RCTs – 2RCTs calcium & vit D vs calcium, 1 RCT vit D only) Vit D supplement doses – 1 RCT 1500µg D_2(600000 IU) single dose, 2RCTs 20µg D_3 (800IU) per day. Mean difference = -0.20 (95%CI -0.39,-0.01) p=0.04, I^2 = 0% ***Timed up and go test*** (3 RCTs calcium & vit D vs calcium) Vit D supplement doses (daily) – 1 RCT 10µg (400IU) D_3, 1 RCT 20µg D_3 (800IU), 1 RCT 25µg (1000IU) D_2 Mean difference = -0.19 (95%CI -0.35,-0.02) p=0.03, I^2 = 0% ***Knee extension strength*** (3 RCTs – 2RCTs calcium & vit D vs calcium, 1 RCT vit D only) Vit D supplement doses - 1 RCT 1500µg D_2(600000 IU) single dose, 1RCT 20µg D_3 (800IU) per day, 1 RCT 25µg (1000IU) D_2 per day Mean difference = 0.05 (95%CI -0.11, 0.20) p=0.04, I^2 = 0%	Postural sway and time to complete the timed up and go task decreased with vitamin D supplementation. Knee extension strength increased with vitamin D supplementation.

Study	Methods	Results	Conclusions
Stockton et al (2011) Effect of vitamin D supplementation on muscle strength: a systematic review and meta-analysis	Selection criteria *Inclusion:* Randomised controlled trials in human adult participants. All forms and doses of vitamin D supplementation with or without calcium supplementation were included compared with placebo or standard care. Outcome measures included evaluation of strength *Exclusion: Not reported* Outcome measure The effect of vitamin D supplementation on muscle strength in adults.	17 RCTs; n=5072; ***Grip strength*** (7 RCTs – 5RCTs calcium & vit D, 2RCTs vit D only) Vit D supplement doses range from 10-25µg (400-1000IU) D3 SMD = -0.02 (95%CI -0.15,0.11) 25OHD>25nmol/l ***Proximal trunk and upper limb strength*** (1 RCT – calcium & vit D) Vit D supplement dose – 20µg (800IU) D3 Bench press SMD = -0.23 (95%CI -0.66, 0.19) baseline 25OHD>25nmol/l Lateral pull downs SMD = -0.32 (95%CI -0.75, 0.10) baseline 25OHD>25nmol/l ***Knee strength*** (7 RCTs – 4RCTs calcium & vit D, 3 RCTs vit D only) Vit D supplement dose – 10-20µg (400-800IU) D3 (daily), 150000µg (600000IU) D3 (single dose), 7500µg (300000IU) D2 (single dose) Knee extension strength SMD = 0.10 (95%CI -0.02, 0.29) 25OHD>25nmol/l Knee flexion strength SMD = 0.10 (95%CI -0.21, 0.41) ***Leg press*** (2 RCTs – calcium & vitamin D) Vit D supplement dose – 20-25µg (800-1000IU) D3 SMD = 0.05 (95%CI -0.26, 0.39) ***Overall proximal lower limb strength*** SMD = 0.1 (95%CI -0.01, 0.22) ***Baseline 25OHD <25nmol/l & proximal lower limb muscle strength*** (2 RCTs) SMD = 3.53 (95%CI 2.18, 4.85)	Vitamin D supplements had no effect on grip strength, proximal trunk and upper limb strength and knee strength. There was no statistically difference in leg press and proximal lower limb strength between the placebo and vitamin D group. Vitamin D supplementation significantly improved proximal lower limb muscle strength in vitamin D deficient subjects.

Study	Methods	Results	Conclusions
Beaudart et al 2014 The effects of vitamin D on skeletal muscle strength, muscle mass and muscle power: a systematic review and meta-analysis of randomized controlled trials	Selection criteria *Inclusion:* RCTs were included if they were published in English, in humans, supplemented with vitamin D, the control group must be comparable to the treated group with the exception of vitamin D supplementation and measured muscle strength, muscle mass or muscle power before and after intervention in both groups. Published from 1966 to January 2014. *Exclusion:* Reviews, trials that are not randomised, duplicated studies, animal studies, studies that did not use a placebo or a control group, or used vitamin D as part of complex nutritional supplementation regimen. Outcome measure Muscle function, including muscle strength, muscle mass and muscle power.	30 RCTs, 5615 participants; mean age 61.1 years (10-99 years); 72% female **Muscle strength** (29 RCTs), 5533 participants SMD 0.17 (95%CI 0.03, 0.31) (p=0.02) **Grip strength** (16 RCTs) SMD 0.01 (95%CI -0.06, 0.07) (p=0.87) **Lower limb** (16 RCTs) SMD 0.19 (95%CI 0.05, 0.34) (p=0.01) **Muscle mass** (6 RCTs) SMD 0.058 (95%CI -0.118, 0.233) (p=0.520) **Muscle power** (5 studies) SMD 0.057 (95%CI -0.194, 0.308) (p=0.657)	There was a small significant positive effect of vitamin D supplementation on muscle strength. No significant effect on muscle mass or muscle power. In sub group analyses participants who presented a 25(OH)D level <30nmol/l resulted in significant higher improvement in muscle strength compared to participants with 25(OH)D >30nmol/l (p=0.02).

SMD – standardised mean difference

Table 23 Randomised controlled trials

Study/year/ Country	Study population/ sample size	Intervention/study design/compliance	Baseline 25OHD (nmol/L) & Analytic method	Post intervention 25(OH)D (nmol/L)	Muscle strength measures	Results	Exclusion criteria/compliance/other comments
Lips et al., 2010 NORTH AMERICA & EUROPE	n=226 Men & women with vitamin D status ≤50 nmol/l ≥15 nmol/l Mean: 78y	1. 210µg (8400IU)/wk vitamin D3 2. Placebo Duration: 16 weeks Double-blind	1. 34.2 ± 11.0 nmol/l 2. 35.2 ± 13.7 nmol/l Reverse phase HPLC	1. 65.4nmol/l 2. Figure not reported, though report that it stayed roughly the same	Postural sway, short physical performance battery (SPPB)	*Change from baseline* SPPB 1. 0.355 (95%CI 0.108,0.601) 2. 0.601 (95%CI 0.351, 0.852) SPPB gait speed test 1. 3.10 (95%CI -0.252, 6.458) 2. 3.94 (95%CI 0.567, 7.38)	Exclusion criteria: primary hyperparathyroidism, active thyroid disease, impaired renal function, osteomalacia, neurologic impairment, peripheral neuropathy, myocardial infarction within 6m of screening, uncontrolled hypertension, postural hypotension, malabsorption syndrome, alcohol abuse or cancer. Treatment with oral glucocorticoids, anabolic steroids, growth hormone within 12m screening, treatment with >800IU vitamin D or with active metabolites of vitamin D with 6m of screening; or treatment with any drug that might affect vitamin D metabolism. Vitamin D: 105/114 completed Placebo: 97/112 completed No significant difference in the change in mediolateral sway and SPPB scores between the intervention and placebo group. In the post hoc analysis of patients subgrouped by baseline sway the mediolateral sway was reduced in the vitamin D supplement group (p=0.047).

Study/year/ Country	Study population/ sample size	Intervention/study design/compliance	Baseline 25OHD (nmol/L) & Analytic method	Post intervention 25(OH)D (nmol/L)	Muscle strength measures	Results	Exclusion criteria/compliance/other comments
Pirotta et al 2014 AUSTRALIA	n=26 >60 years	1. 50µg/d (2000IU) 2.Placebo Duration: 10 weeks Double blind	1. 46.4nmol/l ± 11.4 2. 48.5nmol/l ± 11.1	1. 81nmol/l 2. No change	Knee extensor muscle strength, stair climbing muscle power, balance and gait and timed up and go test.	<u>Knee extension</u> 120^{o} Baseline 1. 0.97 ±0.09 2. 0.96 ±00.6 10 weeks 1. 1.08 ±0.12 2. 1.12 ±0.10 180^{o} 1. 0.75 ±0.09 2. 0.74 ±0.06 10 weeks 1. 0.88 ±0.09 2. 0.84 ±0.09 240^{o} 1. 0.62 ±0.08 2. 0.65 ±0.07 10 weeks 1. 0.77 ±0.09 2. 0.73 ±0.07 <u>Stair climbing</u> Baseline 1. 4.48 ±0.48 2. 4.45 ±0.39 10 weeks 1. 4.14 ±0.26 2. 4.44 ±0.38 <u>Four square step test</u> Baseline 1. 8.68 ±0.45 2. 8.96 ±0.39 10 weeks 1. 8.57 ±0.46 2. 8.68 ±0.38 <u>Timed up and go test</u> Baseline 1. 1.72 ±0.09 2. 1.48 ± 0.15 10 weeks 1. 1.74 ±0.07 2. 1.51 ±0.13	Significant 8-11% increase in muscle strength in the vitamin D group ($p<0.05$), but these changes were not significantly different from the placebo group. There was no effect of vitamin D on muscle power.

Study/year/ Country	Study population/ sample size	Intervention/study design/compliance	Baseline 25OHD (nmol/L) & Analytic method	Post intervention 25(OH)D (nmol/L)	Muscle strength measures	Results	Exclusion criteria/compliance/other comments
Knutsen et al 2014 Norway	Adults 18-50 years Non western immigrant background N=251	1. 10µg/d D3 2. 25µg/d D3 3. Placebo Duration: 16 weeks Compliance 86%	1. 26nmol/l (15) 2. 27nmol/l (16) 3. 27nmol/l (15) Females 1.25nmol/l (15) 2. 27nmol/l (16) 3. 25nmol/l (15) Males 1. 28nmol/l (15) 2. 27nmol/l (15) 3. 29nmol/l (16)	16 weeks 1.43nmol/l (17) 2.52nmol/l (20) 3.25nmol/l (12)	Jumping height, handgrip strength, chair test	Difference (95%CI) compared with placebo <u>Jumping height</u> 1. -2.4 (95%CI -7.2, 2.4) 2. -0.4 (95%CI -5.1, 4.4) Handgrip strength 1. -2.57 (95%CI -7.00, 1.86) 2. 0.21 (95%CI -4.42, 4.85) Chair test 1. -0.53 (95%CI -4.09, 3.04) 2. 0.02 (95%CI -3.97, 4.00)	There was no significant improvement in tests of muscle strength in the vitamin D supplemented groups compared to the placebo groups.

Table 24 - Prospective studies

Reference/Country	Population Description	Follow-up	Muscle strength measure	Mean 25(OH)D (nmol/L) (± SD) baseline	Results
Bolland et al., 2010 AUSTRALIA	Healthy community dwelling postmenopausal women (taking part in a 5y calcium supplement trial) Age: 74y n= 1471	5y	Grip strength	50.5 ± 17.7 nmol/l (seasonally adjusted) 50% <50nmol/l 5.1% <25nmol/l	No association between baseline seasonally adjusted 25OHD and grip strength.
Chan et al., 2012 HONG KONG	Community dwelling men Age: 72.8 ± 5.1y n=714	4y	Grip strength, chair standing time, walking speed & appendicular skeletal muscle mass.	77.9 ± 20.5 nmol/l 5.9% <50.0nmol/l 41.5% 50.0-74.9nmol/l 52.6% ≥75.0nmol/l	No association between baseline 25OHD and change in appendicular skeletal muscle mass, grip strength, chair standing time or walking speed.
Houston et al., 2011 USA	Community dwelling adults Age: 85.2y (77-100y) n= 988; 64.5% female; 16.7% black	3y	SPPB - short physical performance battery (standing balance, repeated chair stand, gait speed scores). Grip and knee extensor strength.	33% ≥75nmol/l 30.8% <50nmol/l	SPPB score significantly lower in participants with deficient 25OHD levels after adjustment for sociodemographic characteristics, season, health behaviours and chronic disease (p=0.006). Grip and knee extensor strength were significantly lower in participants with lower 25OHD levels after adjustment for body weight, sociodemographic characteristics and season (p<0.01) and health behaviours and chronic conditions (p=0.02).
Menant et al., 2012	Community dwelling older people Age: 78y (70-90y) n=463; 53.4% female	1y	Upper and lower limb strength, reaction time, postural sway, gait speed and falls.	62.2± 24.6nmol/l 33.3% <50nmol/l Females – 44% <50nmol/l Males – 21% <50nmol/l	After adjusting for age and BMI subjects with vitamin D insufficiency had weaker strength, slower reaction time, poorer leaning balance and slower gait speed. Vitamin D insufficiency was a significant independent risk factor for falls in men but not women (men IRR 1.93 (95%CI 1.19-3.15) p=0.008).
Scott et al., 2010 AUSTRALIA	Community dwelling older adults (taking part in the Tasmanian Older Adult Cohort Study) Age: 62y ± 7 (50-79y) n= 686; 49% female	2.6y	Appendicular lean mass percentage, leg strength and leg muscle quality.	41.8% ≥50nmol/l	% appendicular lean mass, leg strength, leg muscle quality and physical activity was lower in the subjects with serum 25OHD <50nmol (p<0.05 for all). Following adjustments for confounders baseline 25OHD levels were significantly positively associated with change in leg strength (β=5.74kg 95%CI 0.65, 10.82 p=0.027) and leg muscle quality (β=0.49kg/kg 95%CI 0.17, 0.82 p=0.003).

Reference/Country	Population Description	Follow-up	Muscle strength measure	Mean 25(OH)D (nmol/L) (± SD) baseline	Results
Michael et al 2011 US	Postmenopausal women taking part in the Women's Health initiative Clinical Trial (WHI CT) Age: 70.3 ±3.7	6y	Timed walk and chair-stand tests provided information on gait and dynamic leg strength, respectively. Grip strength is a measure of upper extremity function and has been used as a general indicator of frailty. A physical performance summary score was derived by summing the decile ranking of the best test results for each test per visit.	48.2 ±21.4	Participants with serum 25OHD > 75 nmol/L had significantly higher scores for physical performance (RR 2.64 (95% CI 0.90-4.39) compared to participants with serum 25(OH)D <35nmol/l. Baseline vitamin D had no effect on rate of change in physical performance among women in the study.
Houston et al 2012 US	Men and women taking part in the Health, Aging, and Body Composition Study Age: 71-80y n=2641	2y and 4y	Physical performance and strength. Knee extensor strength Grip strength	1/3 <50nmol/l 2/3 <75nmol/l	Participants with 25(OH)D <50nmol/l had significantly poorer physical performance ($p<0.001$), slower gait speed ($p<0.0001$) and lower knee extensor and grip strength ($p<0.05$) than those with 25(OH)D ≥ 75nmol/l in the cross-sectional analysis. In the longitudinal analysis participants with baseline 25(OH)D <50nmol/l had poorer physical performance and slower gait speed at each time point than those with 25(OH)D ≥75nmol/l ($p<0.01$). Standing balance time and gait speed were associated with baseline 25(OH)D at baseline and 2 and 4 years later ($p\leq0.0001$), but chair stand time was associated with baseline 25(OH)D only 2 and 4 years later ($p<0.05$). Although physical performance and strength declined over 4 years of follow-up ($P < 0.0001$), in general, the rate of decline was not associated with baseline 25(OH)D.

Table 25 Meta-analyses (+/- calcium) ***with further information on mean baseline 25(OH)D concentrations in the included studies***

Study	Methods	Results	Conclusions

Study	Methods	Results	Conclusions
Cameron et al (2012) Interventions for preventing falls in older people in care facilities and hospitals	Selection criteria: *Inclusion:* All randomised trials of falls reduction in older people (≥65y) in nursing care facilities or hospitals, including quasi-randomised trials and those with inadequately concealed treatment allocation. *Exclusion:* Trials that reported only specific types of fall (e.g. injurious falls); trials that focused on intermediate outcomes (e.g. improved balance, strength). Outcome measure • Rate of falls • Number of fallers	**CARE FACILITIES** 6 RCTs (n=5186; mean age 84y; 77% female): 2 used D3, 3 used D2 (2 included Ca); 1 used multivitamin that included vitamin D3 plus Ca (Grieger, 2009). Dose: 5-27.5 µg/d D2 (200-1100 IU), 20 µg/d D3 (800 IU) Baseline 25(OH)D (nmol/L) (mean): Chapuy 2002, 22; Flicker 2005, 25-40 (57% of participants); Bischoff 2003, 30 (median); Broe 2007, 49; Law 2006, 59 (median, 47) (5-95th centile, 35-102); Grieger 2009, 36. (Range: 22-59) Post intervention 25(OH)D: NR ***Rate of falls*** 5 RCTs (n=4605); Rate Ratio (RaR) = 0.63 (0.46-0.86) (I2 = 72%) (Bischoff, 2003; Broe, 2007; Flicker, 2005; Grieger 2009, Law, 2006) Vitamin D + calcium vs calcium 2 RCTs (n=747); RaR = 0.71 (0.56-0.90) (I2 = 0%) (Bischoff, 2003 [D3]; Flicker, 2005 [D2]) Vitamin D2 vs usual care (no placebo) or placebo 2 RCTs (n=3765); RaR = 0.55 (0.19-1.64) (I2 = 80%) (Broe, 2007; Law, 2006) Multivitamins (including D3 + Ca) vs placebo 1 RCT (n=91); RaR = 0.38 (0.20-0.71) (Grieger, 2009) Risk of falling (number of fallers) 6 RCTs (n = 5186); Risk Ratio (RR) = 0.99 (0.90-1.08) (I2 = 12%) Vitamin D + calcium vs calcium 2 RCTs (n=747); RR = 0.85 (0.69-1.05) (I2 = 0%) (Bischoff, 2003; Flicker, 2005) Vitamin D + calcium vs placebo 1 RCT (n=583); RR = 1.03 (0.90-1.18) (Chapuy, 2002) Vitamin D2 vs usual care (no placebo) or placebo 2 RCTs (n=3765); RR = 0.80 (0.38-1.71) (I2 = 58%) Broe, 2007; Law, 2006) Multivitamins (including D3 + Ca) vs placebo 1 RCT (n=91); RaR = 0.82 (0.40-1.66) (Grieger, 2009) HOSPITAL - Risk of falling Vitamin D + calcium vs calcium 1 RCT (n=203); RR=0.82 (0.59-1.14) (Burleigh 2007) Baseline 25(OH)D (nmol/L) (median): 22 nmol/L; IQR = 15.00-30.5	In care facilities, vitamin D supplementation is effective in reducing rate of falls *Authors state: Average serum vitamin D levels at baseline appeared to be low or very low in all 6 studies , therefore these results are only applicable to residents with low vitamin D levels.*

Study	Methods	Results	Conclusions
Gillespie et al (2012) Interventions for preventing falls in older people living in the community	Selection criteria: *Inclusion*: RCTs and quasi-randomised trials of interventions designed to reduce falls in older people (≥60 years) living in the community. Subgroup analysis of the effect if enrolling participants with lower vitamin D status at baseline; 25(OH)D: (Dhesi 2004, ≤30 nmol/L; Pfeifer 2000, 25(OH)D ≤50 nmol/L; Pfeifer 2009, <78; Prince 2008, ≤59.9 nmol/L. *Exclusion*: Trials artificially inducing falls, e.g. during balance testing. Outcome measure • Rate of falls • Number of fallers (risk of falling).	14 RCTs (n=28,135) of vitamin D (D2 [4 trials], D3 [8 trials], not specified [2 trials]) 9 trials - Ca co-supplementation; 2 trials with vitamin D analogues Vit D doses: 10-50 µg/d (400-2000 IU); single 7,500-15,00 µg (300,000-600,000 IU) Baseline 25(OH)D (nmol/L) (mean): Bischoff-Ferrari 2006, 74.7 (SD 38.3); Bischoff-Ferrari 2010, 31.8 (SD 19.6); Dhesi 2004, range 23.7-28; Dukas 2004, 72.6 (SD 27.9); Gallagher 2001, 79.3 (SD 24.7); Grant 2005, 38.8 (SD 15.6); Harwood 2004, 29.5 (range 6-85); Karkkainen 2010, 49.7; Latham 2003, IG-37.4 (95% CI 34.9-44.9), CG-47.4 (95% CI 39.9-52.4); Pfeifer 2000, 25.2 (SD 12.9); Pfeifer 2009, 54.5 (SD 18); Porthouse 2005, NA; Prince 2008, 44.8 (SD 12.7); Sanders 2010, NA; Smith 2007, NA; Trivedi 2003, NA. (Range: 24-79) Post intervention 25(OH)D: NR **Vitamin D (+/- calcium) vs control/placebo/calcium** ***Rate of falls*** 7 RCTs (n=9324); Rate Ratio (RaR) = 1.0 (0.90-1.11) 2 RCTs (n=2478) vitamin D vs control or placebo; RaR = 1.14 (1.03-1.27) 3 RCTs (n=6586) vitamin D + Ca vs control or placebo; RaR = 0.96 (0.89-1.04) 1 RCT vitamin D + Ca vs Ca (n=137); **RaR = 0.54 (0.30-0.98)** ***Risk of falling (fallers)*** 13 RCTs (n=26,747); Risk Ratio (RR) = 0.96 (0.89-1.03) 3 RCTs (n=4516) vitamin D vs control or placebo; RaR = 1.08 (0.93-1.276) 3 RCTs (n=6576) vitamin D + Ca vs control or placebo; RaR = 0.98 (0.92-1.03) 2 RCTs vitamin D + Ca vs Ca (n=379); **RaR = 0.70 (0.53-0.28)** **Participants with lower vitamin D concentrations** ***Rate of falls*** 2 RCTs selecting on 25(OH)D status (≤ 50 nmol/L) (n=260); **RaR = 0.57 (0.37-0.89)** *(Dhesi, 2004 [24-28 nmol/L]; Pfeifer, 2000 [25 nmol/L])* 5 RCTs not selecting participants on 25(OH)D status (n=9064); RaR = 1.02 (0.88-1.13) ***Risk of falling (fallers)*** 4 RCTs selecting on 25(OH)D status (≤ 78 nmol/L) (n=562); **RR = 0.70 (0.56-0.87)** *(Dhesi, 2004 24-28 nmol/L; Pfeifer, 2000 [25 nmol/L]; Pfeifer, 2009 [55 nmol/L]; Prince, 2008 [45 nmol/L])* 9 RCTs not selecting participants on 25(OH)D status (n=25,943); RR = 1.00 (0.93-1.07)	Overall, vitamin D supplementation does not appear to reduce falls but may be effective in people who have lower vitamin D levels before treatment.

Study	Methods	Results	Conclusions
Kalyani et al (2010) Vitamin D treatment for the prevention of falls in older adults: systematic review and meta-analysis	Selection criteria: *Inclusion*: RCTs comparing vitamin D treatment with either calcium therapy, placebo, or no treatment; mean age ≥ 60 years; number of participants with ≥ 1fall by treatment arm stated; explicit definition of fall; description of how falls were ascertained. *Exclusion*: Studies that used intramuscular vitamin D; studies restricted to participants with significant neurological disabilities (e.g., Parkinson's disease or stroke with hemiplegia). Outcome measure • Number of participants with one or more falls during follow-up.	10 RCTs (n=2932; mean age 71-92y) of: D3 (6); D2 (3); 7 with Ca co-supplementation; 1 trial with vitamin D analogue Treatment duration: 1-36 months; Dosage: 5-25 µg (200-1000 IU) Baseline 25(OH)D (nmol/L) (mean): Burleigh 2007, IG-22.5/CG-25; Pfeifer 2000, 26; Bischoff 2003, 30; Flicker 2005, 40 (median); Broe 2007, 42/45/52; Prince 2008, 45; Pfeifer 2009, 55; Bischoff-Ferrari 2006, 66(f)/82(m); Dukas 2004, 75; Graafmans 1996, NR. (Range: 23-82) Post intervention 25(OH)D: NR ***Number of falls*** 10 RCTs (n=2932); **Relative Risk (RR) = 0.86 (0.79–0.93) (I^2=7%, p=0.38*)*** *Subgroup analysis by adjunctive calcium supplementation* Vitamin D alone*:* 3 RCTs (n=856); RR = 0.94 (0.77–1.15) *(Graafmans, 1996; Broe, 2007; Dukas, 2004)* Vitamin D & calcium: 7 RCTs (n=2076); **RR = 0.83 (0.75–0.92)** *(Burleigh, 2007; Pfeifer, 2000; Bischoff, 2003; Flicker, 2005; Prince, 2008; Pfeifer, 2009; Bischoff-Ferrari, 2006).* *Subgroup analyses by vitamin D dose* Dose < 20 µg/d (800 IU): 3 RCTs (n=950); RR = 1.01 (0.85-1.20) *(Graafmans, 1996; Broe, 2007; Bischoff-Ferrari, 2006)* Dose ≥ 20 µg/d (800 IU): 7 RCTs (n=1679); **RR = 0.80 (0.70-0.91)** *(Pfeifer, 2000; Flicker, 2005; Pfeifer, 2009; Burleigh, 2007; Bischoff, 2003; Prince, 2008; Broe, 2007)* *Did not reach statistical significance (intergroup, p=0.06)* Significant reduction in no. of falls also found in following subgroups: community-dwelling (aged <80y); no history of fractures or falls; treatment duration > than 6 months.	Vitamin D treatment effectively reduces risk of falls in older adults. *Authors state that they were not able to investigate whether the treatment of vitamin D on fall prevention would also apply to populations that were not vitamin D deficient at baseline since all included studies had vitamin D levels that were less than 75 nmol/L.*

Study	Methods	Results	Conclusions
Murad et al (2011) Clinical review: The effect of vitamin D on falls: a systematic review and meta-analysis	Selection criteria: *Inclusion*: Randomised trials with adults who received vitamin D supplementation and comparison group that did not receive intervention. Studies included regardless of size or duration of follow-up. *Exclusion*: Studies using $1,25(OH)_2D$ or one of its analogues. Outcome measure Risk of at least 1 fall, i.e. fallers.	26 RCTs (n=45,782; mean age 76y; 78% female): D3 (12); D2 (9); D (5); 15 with Ca co-supplementation Treatment duration: 3-62 months Baseline 25(OH)D (nmol/L) (did not specify if mean or median): 17 out of 26 studies reported baseline 25(OH)D concentrations: Witham 2010, 20.7; Chapuy 2002, 21.2 (13); Dhesi 2004, 26; Bischoff 2003, 31; Chapuy 1992, 40; Latham 2003, 42.2; Broe 2007, 48.7; Sanders 2010, 52.4; Burleigh 2007, 55; Pfeifer 2009, 55; Prince 2008, <60; Pfeifer 2000, 61.5 (30.3); Flicker 2005, 62.4-224.6; Harwood 2004, 70-75; Bischoff-Ferrari 2006, 70-82.4; Sato 2005, 71; Law 2006, 117.3. (Range 21-225) 9 studies did not report baseline concentrations: Arden 2006; Berggren 2008; Graafmans 1996; Grant 2005; Karkkainen 2009; Larsen 2005; Peichl 1999; Porthouse 2005; Trivedi 2003. Post intervention 25(OH)D (nmol/L): Witham 2010, NR; Chapuy 2002, NR; Dhesi 2004, 43.7; Bischoff 2003, 65.4; Chapuy 1992, 104.8; Latham 2003, NR; Broe 2007, 59.9-74.9; Sanders 2010, 54.9-74.1; Burleigh 2007,NR; Pfeifer 2009, 84; Prince 2008, 152.3; Pfeifer 2000, NR; Flicker 2005, NR; Harwood 2004, 99.8-124.9; Bischoff-Ferrari 2006, 102-110; Sato 2005, 67.8; Law 2006, 184.7; (Range: 44-185) ***Risk of at least 1 fall, i.e. fallers*** 26 RCTs; **OR = 0.86 (0.77-0.96) (I^2= 66%)** (substantial heterogeneity) *Subgroup analysis by calcium co-administration†* Vitamin D + calcium vs placebo: 10 trials; **OR = 0.83 (0.72– 0.93)** Vitamin D vs. placebo: 10 trials; OR = 0.97 (0.84 –1.11) Vitamin D + calcium vs calcium: 10 trials; **OR = 0.63 (0.50–0.81)** *Subgroup analysis by vitamin D dose†* High dose (> 20 µg/800 IU/d); 18 trials; **OR = 0.82 (0.73– 0.93)** Low dose (< 20 µg/800 IU/d); 8 trials; OR = 1.00 (0.72–1.37) *Subgroup analysis by baseline vitamin D deficiency status*†* Not deficient: 20 trials; **OR = 0.90 (0.81– 0.99)** Deficient: 6 trials; **OR = 0.53 (0.39–0.72)** ***Number of falls*** **OR = 0.79 (0.70-0.88) (I^2= 90%)** †Did not specify the trials included in the subgroup analyses *Not specified. Based on author description of population, reported baseline serum level of 25(OH)D or enrolment of patients with at least 2 vitamin D deficiency risk factors (older, age, dark skin, living in nursing home, living far from equator, winter season, sunscreen use, wearing veil, smoking, obesity, malabsorption disease, renal or liver disease, use of medication such as anticonvulsants, glucocorticosteroids, HIV medications).	Vitamin D combined with calcium reduces risk of falls. Fall reduction in studies without calcium coadministration did not reach statistical significance.

Study	Methods	Results	Conclusions
Bolland et al 2014	Selection criteria: *Inclusion*: randomised trials that studied vitamin D supplementation with outcome data for falls published since Jan 2009. *Exclusion:* cluster randomised trials, trials of hydroxylated vitamin D or vitamin D analogues, trials that included other interventions only in the vitamin D group, and trials in populations with chronic comorbidity other than osteoporosis or frailty. Outcome measure Falls	20 RCTs (n=29,535) Vitamin D 0.95 (95%CI 0.89, 1.02) Vitamin D and calcium 0.95 (95%CI 0.89, 1.03) Vitamin D with/without calcium 0.96 (95%CI 0.91, 1.01)	No effect of vitamin D supplementation, with or without calcium, on risk of falls.

NR, not reported

Table 26 Randomised Controlled Trials

Reference / Country	Study Design/Population/ Exclusion criteria	Intervention/compliance/duration	Baseline mean 25(OH)D (nmol/L)(±SD)/Analytical method/Ca intake	Post-intervention mean 25(OH)D (nmol/L) (±SD)	Number of falls	RR/OR (95%CI) Intervention group vs control group	Comments	Conclusion
Sanders et al (2010) Annual high-dose oral vitamin D and falls and fractures in older women AUSTRALIA	n = 2,256 Women (community dwelling; at high risk of fracture) Median age (IQR) IG: 76.0 (73.1-80.2) CG: 76.1 (73.0-79.7); Exclusion criteria: could not give informed consent/info about falls/fractures; resident at high-level care facility; Ca > 2.65 mmol/L, creatinine > 150 μmol/L; vit D intake ≥ 10 μg/d, calcitriol, or anti-fracture therapy.	IG: 12,500 μg (500,000 IU) D_3 – single dose annually CG: placebo Compliance: not stated Duration: 3 to 5 years Randomised Double-blind Placebo-controlled	*Median (IQR)* All: 49 (40-63) (n=131) IG: 53 (40-65) (n=74) CG: 45 (40-57) (n=57) RIA (Diasorin)	12m post-dose: 74 nmol/L or higher IG: 9.5% CG:5.3% 51-74nmol/L IG: 44.5 CG:33.32 26-50 nmol/L IG: 41.9% CG: 57.9% 25nmol/L or less: IG: 4% CG: 3.5%	At least 1 fall IG: 837/1131 (74%) CG: 769/1125 (68% Cumulative incidence of 1st fall; Hazard ratio = 1.16 (1.05-1.28)	Incidence rate ratio = 1.15 (1.02-1.30)	IG experienced 15% more falls than the CG. Observed temporal risk pattern - increased likelihood of falls in IG group exacerbated in the 3-month period immediately following annual dose.	Annual oral administration of high-dose vitamin D_3 increased risk of falls.

Control group (CG); Intervention group (IG); Odds ratio (OR); Risk Ratio (RR); Rate ratio (RaR).

Table 27 Cohort studies

Reference/Country	Population Description	Follow-up	Mean 25(OH)D (nmol/L) (± SD) baseline	Results	Comments
Menant et al., 2012	Community dwelling older people Age: 78y (70-90y) n=463; 53.4% female	1y	62.2± 24.6nmol/l 33.3% <50nmol/l Females – 44% <50nmol/l Males – 21% <50nmol/l	Men IRR 1.93 (95%CI 1.19, 3.15) (p=0.008) Women IRR 0.83 (95%CI 0.56, 1.23) (p=0.362)	Vitamin D insufficiency significantly increased the rate of falls in men but not in women.

NON-MUSCULOSKELETAL HEALTH OUTCOMES

Pregnancy and lactation: non skeletal outcomes in mother and baby
Table 28 Systematic review

Study	Methods	Results	Conclusions
Harvey et al 2014 Vitamin D supplementation in pregnancy: a systematic review	Selection criteria: *Inclusion:* pregnant women or pregnant women and their offspring, RCTs, cohort studies, case control studies *Exclusion:* ecological and animal studies, not written in English, did not measure maternal vitamin D status in or immediately after pregnancy, or supplement participants with vitamin D in pregnancy, or where an outcome of interest was not assessed. Outcome measure Primary: Neonatal hypocalcaemia, rickets in the offspring and offspring bone mass; maternal osteomalacia; Secondary: Offspring body composition (birth weight, birth length, head circumference, anthropometry, risk of being born small for gestational age, risk of low birth weight); offspring preterm birth and later offspring health outcomes (including asthma and atopy, blood pressure and Type 1 diabetes); maternal quality of life (including preeclampsia, gestational diabetes, risk of caesarean section and bacterial vaginosis).	Birth weight and length 9 RCTs: n= 40-350 1st meta-analysis inc: Brooke et al 1980, Marya et al 1981, Congdon et al 1983, Mallet et al 1986 & Kaur et al 1991 Mean weighted difference 116.23g (95%CI -57, 289.5) 2nd meta-analysis inc: Brooke et al 1980, Marya et al 1981, Congdon et al 1983, Mallet et al 1986, Marya et al 1988, Kaur et al 1991 Mean weighted difference 147.3g (95%CI -112.5, 407.15) 19 observational studies (5 cross-sectional, 14 cohort studies) 1st meta-analysis using log transformed units: Harvey et al 2008, Gale et al 2008, Farrant et al 2009 Change in birth weight per 10% increase in vitamin D 5.63 (95%CI 1.11, 10.16) Preeclampsia 11 observational studies (4 cohorts, 6 case-control, 1 cross sectional study) Meta-analysis of 4 studies: Bodnar, Powe, Robinson & Aar OR 0.78 (95%CI 0.59, 1.05) Maternal gestational diabetes 8 observational studies (3 cohorts, 4 case-control, 1 cross-sectional study)	There was no significant difference in birth weight between supplemented and unsupplemented groups. No significant increased risk of preeclampsia with decreased vitamin D status. No significant association between 25(OH)D and maternal gestational diabetes.

Table 29 Intervention studies

Author /year/ location	Population	Design	Intervention	250HD Maternal/ infant baseline (nmol/L)	25OHD cord (nmol/L)	Comments
Effect of vitamin D supplements during pregnancy on serum/plasma 25(OH)D concentration						
Cockburn et al 1980 Edinburgh n=1139 (n=506 received intervention, 633 controls)	Pregnant women	Non-RCT	1. 10µg/d D2 2. Placebo Duration: 12th week of pregnancy to gestation.	24 weeks 1. 39nmol/L 2. 32.5nmol/L 34 weeks 1. 44.5nmol/L 2. 38.5nmol/L Delivery 1. 42.8nmol/L 2. 32.5nmol/L	1. 28nmol/L 2. 20nmol/L Infant capillary (day 6) 1. 34.5nmol/L 2. 20.3nmol/L	Plasma 25(OH)D concentration was higher in the pregnant women receiving the vitamin D supplement.
Brooke 1981 London n = 126	South Asian women in their last trimester.	RCT	1. 25µg/day 2. Placebo Duration: throughout last trimester of pregnancy	1. 168nmol/L 2. 16nmol/L	1. 138 (SE = 10.8) 2. 10 (SE = 2.0)	There was a significant increase in serum 25(OH)D concentration between baseline sample concentration and delivery.
Hollis et al 2011 S. Carolina US n=350	Pregnant women 12-16 weeks gestation.	RCT	1. 10µg/d 2. 50µg/d 3. 100µg/d	1. 79nmol/L (SD = 86) 2. 98nmol/L (SD = 34) 3. 111nmol/L (SD = 40)	1. 45nmol/L (SD = 25) 2. 57nmol/L (SD = 25) 3. 66nmol/L (SD = 26)	Mean circulating 25(OH)D one month prior to delivery and at delivery was statistically different between treatment groups, with the highest mean level achieved in the 100µg/d group.

Author /year/ location	Population	Design	Intervention	250HD Maternal/ infant baseline (nmol/L)	25OHD cord (nmol/L)	Comments
Yu et al 2009 London	Pregnant women recruited at 27 weeks gestation. n=180 Indian Asian, Middle Eastern, Black and Caucasian.	RCT	1. Single dose 5000µg 2. 20µg/d 3. No treatment Duration: 27 weeks to delivery	At 27 weeks (median) 1. 26nmol/L 2. 26nmol/L 3. 25nmol/L At delivery (median) 1. 34nmol/L 2. 42nmol/L 3. 27nmol/L	Median 1. 25nmol/L 2. 26nmol/L 3. 17nmol/L	Maternal 25(OH)D were significantly higher in the supplemented groups compared to the control group.
Congdon et al 1983 Leeds	Pregnant Asian women. n=64 Asian women, 12 white women	Controlled study	1. 25µg/d n=19 Asian women 2. No treatment n=45 Asian women 3. No treatment n=12 white women	Not reported.	1. 15.2nmol/L (3.15) 2. 5.9nmol/L (0.93) 3. 33.4nmol/L (3.6)	
Datta et al 2002 South Wales	Pregnant women from a non-European ethnic minority population in South Wales supplemented with vitamin D if 25(OH)D concentration <20nmol/L. n=160 (Indian subcontinent, Afro-Caribbean, Middle East, Far East, Africa)	Uncontrolled study	20µg/d if 25(OH)D concentration was below 20nmol/L. At 36 weeks if 25(OH)D concentration was still low the women were supplemented with 40µg/d.	14.5nmol/L 58 out of 80 women were treated with vitamin D supplements during pregnancy.	Post delivery 28nmol/L 58 out of 80 women were treated with vitamin D supplements during pregnancy	Women from ethnic minority populations in South Wales were subclinically deficient in vitamin D.
Delvin et al 1986 Lyon	Pregnant women at the end of 1st trimester n=40	RCT	1. 25µg/d D3 2. No treatment	1. 45nmol/L (5) 2. 17.5nmol/L (2.5)	1. 32.5nmol/L (2.5) 2. 12.5nmol/L (2.5) (serum concentration 4days after birth)	At delivery cord blood 25(OH)D concentration was higher in the supplemented group.
Neonatal hypocalcaemia						

Author /year/ location	Population	Design	Intervention	250HD Maternal/ infant baseline (nmol/L)	25OHD cord (nmol/L)	Comments
Cockburn 1980 Edinburgh	Pregnant women n=1139 Ethnicity not stated	Non-RCT	1. 10µg/d D2 2. Placebo Duration: from 12 weeks of pregnancy to delivery	At 24 weeks 1. 39nmol/L 2. 32.5nmol/L At 34 weeks 1. 44.5nmol/L 2. 38.5nmol/L At delivery 1. 42.8nmol/L 2. 32.5nmol/L	3. 28nmol/L 4. 20nmol/L	Neonatal hypocalcaemia (defined as plasma Ca^{2+} < 1.85 mmol/L) occurred in 6% of the intervention group infants and 13% of controls (p < 0.005).
Brooke 1981 London	South Asian women in their last trimester. n = 126	RCT	3. 25µg/day 4. Placebo Duration: throughout last trimester of pregnancy	3. 168nmol/L 4. 16nmol/L	3. 138 (SE = 10.8) 4. 10 (SE = 2.0)	Five control infants but no treatment group infants developed symptomatic hypocalcaemia (plasma Ca2+ < 1.8 nmol/L). The 25OHD concentrations in cord and maternal plasma greatly exceed those observed in other studies.
Delvin et al 1986 Lyon	Pregnant women at the end of 1st trimester n=40	RCT	3. 25µg/d D3 4. No treatment	3. 45nmol/L (5) 4. 17.5nmol/L (2.5)	3. 32.5nmol/L (2.5) 4. 12.5nmol/L (2.5) (serum concentration 4days after birth)	There was a significant difference (p<0.002) in serum calcium at 4 days of age in both groups although to a lesser extent in infants born to the supplemented mothers (p<0.05).
Birth weight and length, small for gestational age						
Wagner et al 2013a US	Pregnant women 12-16 weeks gestation n=257	RCT	1. 50µg/d 2. 100µg/d	56.7nmol/L	1. 61.2nmol/L 2. 55.2nmol/L	There was no difference in birth weight, gestation or neonatal health between the two groups.

Author /year/ location	Population	Design	Intervention	250HD Maternal/ infant baseline (nmol/L)	25OHD cord (nmol/L)	Comments
Maternal non-skeletal reproductive outcomes						
Marya et al 1987 India	Pregnant women attending an antenatal clinic in India n=400	RCT	1. 30µg vitamin D & 375mg/d calcium 2. No treatment From 20-24 weeks gestation until delivery	Not measured	Not measured	12 cases of preeclampsia in intervention group and 18 cases in the control group. This result was not significant.
Hollis et al 2011 S. Carolina US	Pregnant women 12-16 weeks gestation. n=350	RCT	4. 10µg/d 5. 50µg/d 6. 100µg/d	79 (SD = 86) 98 (SD = 34) 111 (SD = 40)	45 (SD = 25) 57 (SD = 25) 66 (SD = 26)	No statistical significant effect of daily vitamin D3 supplementation (10 µg/400 IU; 50 µg/2000 IU; or 100 µg/4000 IU) on risk of instrumental delivery; however, there was no unsupplemented control group.
Maternal serum 25(OH)D concentrations in pregnancy, fetal/ infant "stores" and breastfeeding						
Gallo et al 2013a Canada	Infants age 1 month n=52	RCT	1. 10µg/d D2 2. 10µg/d D3 Duration: 4months	1. 68.3nmol/L (21.4) 2. 69.5nmol/L (21.7) Infant baseline (LC-MS/MS) 1. 44.2nmol/L (23.8) 2. 54.6nmol/L (23.7)	Infants aged 4 months 1. 64.8nmol/L (26.2) 2. 76.8nmol/L (17.4)	The increase in the 25(OH)D concentration among the D2 and D3 groups did not differ.

Author /year/ location	Population	Design	Intervention	250HD Maternal/ infant baseline (nmol/L)	25OHD cord (nmol/L)	Comments
Gallo, Comeau et al 2013 Canada	Healthy, term, breastfed infants. n=132	RCT	1. 10µg/d 2. 20µg/d 3. 30µg/d 4. 40µg/d	Not reported	% of infants achieving 75nmol/L at 3 months 1. 55% 2. 81% 3. 92% 4. 100%	25(OH)D concentrations increased in all infants
Maternal 25(OH)D concentration and later growth						
Brooke et al 1981 UK	South Asian women in their last trimester. n = 126	RCT	1. 25µg/day 2. Placebo Duration: throughout last trimester of pregnancy	1. 168nmol/L 2. 16nmol/L	1. 138 (SE = 10.8) 2. 10 (SE = 2.0)	At age 1 year there was no significant difference in head circumference between the two groups.

Table 30. Observational studies

Reference/ country	Population description	Follow up	Mean 25(OH)D	Results	Comments
Birth weight and length, small for gestational age					
Haggarty et al 2013 Aberdeen, Scotland	Pregnant women at around 19 weeks gestation. n=1205 3% non caucasian	19 weeks gestation to delivery	Maternal All seasons – 40.2nmol/L Winter – 34.4nmol/L Spring – 39.7nmol/L Summer – 53.1nmol/L Autumn – 33.7nmol/L Cord blood All seasons – 21.8nmol/L Winter – 13.6nmol/L Spring – 23.1nmol/L	Not reported	There was no significant relationship between maternal or cord plasma 25(OH)D concentration and birth weight or standardised birth weight, with or without adjustment for the level of deprivation.

			Summer – 33.4nmol/L Autumn – 19.4nmol/L		
Bodnar et al 2010 US	Pregnant women who delivered small for gestational age infants. *White women* 22 cases 23 controls *Black women* 20 cases 19 controls	<16 weeks gestation to delivery	*White women* <37.5nmol/L: 8 cases, 3 controls 37.5 – 75nmol/L: 27 cases, 107 controls >75nmol/L: 42 cases, 86 controls *Black women* <37.5nmol/L: 17 cases, 48 controls 37.5-75nmol/L: 13 cases, 50 controls >75nmol/L: 4 cases, 7 controls	*White women* <37.5nmol/L OR 7.5 (95%CI 1.8, 31.9) 37.5-75nmol/L OR 1.0 ref >75nmol/L OR 2.1 (95%CI 1.2, 3.8) *Black women* <37.5nmol/L OR 1.5 (95%CI 0.6, 3.5) 37.5-75nmol/L OR 1.0 ref >75nmol/L OR 2.2 (95%CI 0.5, 9.0)	A U-shaped association was observed between serum 25(OH)D concentration and risk of delivering an SGA infant, with a significantly increased risk among white mothers with serum 25(OH)D concentration < 37.5 nmol/L and > 75nmol/L). No association was found between serum 25(OH)D concentration and SGA risk among black mothers.
Morley et al 2006	Pregnant women before 16 weeks gestation. n=374	28-32 weeks gestation to delivery	Maternal 25(OH)D concentration at 28-32 weeks <28nmol/L = 7 ≥28nmol/L = 347	Gestation length (weeks) Difference -0.8 (95%CI -1.4, 0.2) Knee-heel length (mm) Difference -4.5 (95%CI-7.5, -1.5) Birth weight (9g) Difference -153 (95%CI -348, 42) Head circumference (cm) Difference -0.2 (95%CI -0.8, 0,3)	There was no association between maternal plasma 25(OH)D concentration at 11 weeks gestation and birth size or weight but women with plasma 25(OH)D concentration < 28 nmol/L at 28-32 weeks gestation delivered significantly earlier. Their babies' knee-heel distance was also significantly shorter and a small difference persisted even after adjustment for gestation length.
Burris et al 2012 US	Participants in the Project Viva cohort study of gestational factors and offspring health. n=1067 white mothers	2nd trimester to delivery.	2nd trimester 60nmol/L White mothers – 62nmol/L (20nmol/L) Black mothers – 46nmol/L (22nmol/L)	Small for gestational age <25 vs ≥25nmol/L OR 3.17 (95%CI 1.16, 8.63)	There was a higher risk of an infant small for gestational age with mothers with a low 25(OH)D concentration.

	n=236 black mothers				
Later cognitive and psychological development					
Gale et al 2008 Southampton	Pregnant women at 17 weeks gestation in the Southampton's Women's Survey n =466	17 weeks gestation to infant aged 9 years	50nmol/L (median) (30-75.3) <27.5nmol/L 21.2% 27.5-50nmol/L 28.3% >50nmol/L 50.4%	Total difficulties <30nmol/l OR 1.0 Ref -50nmol/L OR 2.11 (95%CI 0.59, 7.62) -75nmol/L OR 2.44 (95%CI 0.69, 8.64) >75nmol/L OR 0.75 (95%CI 0.16, 3.58)	There was no association between maternal 25(OH)D concentration and cognitive function, psychological health.
Whitehouse et al 2012 Western Australia	Caucasian pregnant women at 18 weeks gestation n=743	18 weeks gestation	Q1 36.8nmol/L (15-46nmol/L) = 187 subjects Q2 53.1nmol/L (47-59nmol/L) = 189 subjects Q3 65.1nmol/L (60-71nmol/L) = 182 subjects Q4 83.5nmol/L (72-154nmol/L) = 185 subjects	Maternal 25(OH)D concentration association with language impairment during childhood Q4 OR 1.0 Ref Q3 OR 1.44 (95%CI 0.74, 2.8) p=0.28 Q2 OR 1.35 (95%CI 0.71, 2.57) p=0.36 Q1 OR 1.97 (95%CI 1.00, 3.93) p<0.05	There was a significant increased risk of women with 25(OH)D concentrations <46nmol/L during pregnancy having a child with clinically significant language difficulties compared to 25(OH)D concentrations >75nmol/L.
Maternal 25(OH)D concentration and later growth					
Gale et al 2008 Southampton	Pregnant women at 17 weeks gestation in the Southampton's Women's Survey n =466	17 weeks gestation to infant aged 9 years	50nmol/L (median) (30-75.3) <27.5nmol/L 21.2% 27.5-50nmol/L 28.3% >50nmol/L 50.4%	Head circumference at 9 year <30nmol/L 52.6 cm -50nmol/L 53.2cm -75nmol/L 53.4cm >75nmol/L 53.6cm P=0.012	Head circumference was significantly greater at age 9 years in the offspring of mothers with serum 25(OH)D concentration >75 vs< 30nmol/L in the third trimester.
Respiratory disease					
Gale et al 2008 Southampton	Pregnant women at 17 weeks gestation in the Southampton's Women's Survey n =466	17 weeks gestation to infant aged 9 years	50nmol/L (median) (30-75.3) <27.5nmol/L 21.2% 27.5-50nmol/L 28.3% >50nmol/L 50.4%	Reported asthma at 9 years <30nmol/L OR 1.0 Ref -50nmol/L OR 2.05 (95%CI 0.36, 11.8) -75nmol/L	No association between maternal 25(OH)D concentrations and risk of asthma at 9 years.

	OR 2.05 (95%CI 0.36, 11.8) >75nmol/L OR 5.40 (95%CI 1.09, 26.6)

Table 31: Meta analyses

Study	Methods	Results	Conclusions
Total cancer			
Keum & Giovannucci (2014) Vitamin D supplements and cancer incidence and mortality: a meta-analysis	Selection criteria: *Inclusion*: studies had to be a RCT providing information on the effect of vitamin D supplementation (with or without calcium supplementation) on total cancer incidence or mortality. *Exclusion:* abstracts and unpublished results Outcome measure Total cancer incidence	Total cancer incidence: 4 RCTs; 4333 cases & 45151 participants. RR 1.00 995%CI 0.94, 1.06) p=0.998 Total cancer mortality: 3 RCTs; 1190 deaths & 44260 participants. RR 0.88 (95%CI 0.78, 0.98) p=0.02	Vitamin D supplementation had no significant effect on total cancer incidence. Vitamin D supplementation had a significant effect on cancer mortality.
Colorectal cancer			
Gandini et al (2011) Meta-analysis of observational studies of serum 25-hydroxyvitamin D levels and colorectal, breast and prostate cancer and colorectal adenoma	Selection criteria: *Inclusion*: case-control and cohort studies published as an original article, which reported relative risk estimates or crude data for serum 25-hydroxyvitamin D levels. *Exclusion*: Studies reporting data from predictive models or serum 1a,25-dihydroxyvitamin D levels only were excluded. Ecological studies, case reports, reviews and editorials were not considered eligible. Outcome measure Colorectal cancer	9 studies, 2630 cases Per 25nmolL increase RR 0.85 (95%CI 0.79, 0.92)	There was a significant inverse relationship between serum 25(OH)D concentration and colorectal cancer risk.
Breast cancer			

Study	Methods	Results	Conclusions
Sperati et al 2013 Vitamin D supplementation and breast cancer prevention: a systematic review and meta-analysis of randomized clinical trials	Selection criteria: *Inclusion:* RCTs of vitamin D and breast cancer. RCTs had to administer a single agent compared with placebo/no treatment or as part of combined regimens including supplements and lifestyle modifications as long as the administration of the co-intervention was planned to be the same in all groups. For multi-arm RCTs, all pairwise comparisons with arms differing by vitamin D use only were included. Breast cancer incidence and mortality were the outcomes of interest in RCTs focused on breast cancer prevention. *Exclusion:* RCTs involving pregnant or lactating women. Outcome measure Breast cancer prevention.	2 trials, 5372 postmenopausal women. 20-27.5µg/d (800-1100IU/d) RR 1.11 (95%CI 0.74, 1.68).	No effect of vitamin D supplementation on risk of breast cancer
Kim and Je (2014) Vitamin D intake, blood 25(OH)D levels, and breast cancer risk or mortality: a meta-analysis	Selection criteria: *Inclusion:* presented original data from cohort or nested case-control studies; outcome of interest defined as breast cancer incidence or mortality from breast cancer or all-cause mortality among breast cancer patients; exposure of interest was vitamin D intake or blood 25(OH)D levels; and studies provided relative risks and their confidence intervals. *Exclusion:* not reported Outcome measure Breast cancer risk or mortality	**Breast cancer risk** – 13 nested case control studies, 1 cohort study, 9526 cases Highest 25(OH)D concentration (>31ng/ml) vs lowest (<18ng/ml) RR 0.92 (95%CI 0.83, 1.02) p=0.16 Highest intake (>5000IU/d) vs lowest (<148IU/d) RR 0.95 (95%CI 0.88, 1.01) p=0.09 Increment of 10ng/ml RR 0.98 (95%CI 0.96, 1.00) **Breast cancer mortality** – 6 prospective studies, 301 deaths from breast cancer among 4556 patients Highest 25(OH)D concentration (>29.1ng/ml) vs lowest (<21ng/ml) RR 0.58 (95%CI 0.40, 0.85) Increment of 10ng/ml RR 0.88 (95%CI 0.79, 0.98)	There was a non significant inverse association between vitamin D intake or 25(OH)D levels and breast cancer risk. Among breast cancer patients high 25(OH)D levels were significantly associated with low risk of death from breast cancer decreasing by 42% for high (>29.1ng/ml) vs low (<21ng/ml).
Prostate cancer			

Study	Methods	Results	Conclusions
Gilbert et al (2011) Associations of circulating and dietary vitamin D with prostate cancer risk: a systematic review and dose-response meta-analysis	Selection criteria: *Inclusion:* Peer reviewed papers that presented primary epidemiological data reporting prostate cancer incidence and either: circulating blood plasma or serum concentrations of either of the 2 main vitamin D metabolites (25(OH)D & 1,25$(OH)_2$D) or dietary &/or supplement vitamin D intake. Subjects must have circulating blood vitamin D measurement taken prior to cancer diagnosis. *Exclusion:* Abstracts and letters. Papers not presenting primary data, animal or case studies. Papers reporting benign prostatic hyperplasia as only outcome and papers with subjects given vitamin D in conjunction with chemotherapy. Studies that assessed the effect of vitamin D on prostate cancer survival. Outcome measure Prostate cancer	**25(OH)D meta-analysis** 14 cohort/nested case control studies total prostate cancer (4353 cases) & 6 studies for aggressive prostate cancer (871 cases); Total prostate cancer per 10ng/ml increase OR 1.04 (95%CI 0.99, 1.10) (p=0.12) Aggressive prostate cancer per 10ng/ml increase OR 0.98 (95%CI 0.84, 1.15) (p=0.78)	No association between 25(OH)D concentration and total and aggressive prostate cancer.
Ovarian cancer			
Yin et al (2011) Meta-analysis: Circulating vitamin D and ovarian cancer risk	Selection criteria: *Inclusion:* Original longitudinal studies conducted among humans. *Exclusion:* Editorials, comments, reviews, ecological studies, only vitamin D intake reported, only mortality among ovarian cancer patients assessed, case control studies and repeated studies from the same study population. Outcome measure Ovarian cancer incidence and mortality.	10 longitudinal studies, 2488 subjects including 883 ovarian cancer cases. Per 50nmol/L increase in 25(OH)D RR 0.83 (95%CI 0.63, 1.08) p=0.16	No significant association between 25(OH)D concentration and ovarian cancer.

Study	Methods	Results	Conclusions
Non melanoma skin cancer			
Caini et al 2014 Vitamin D and melanoma and non-melanoma skin cancer risk and prognosis: A comprehensive review and meta-analysis	Selection criteria: *Inclusion:* papers investigating the association between either blood levels or dietary intake of 25(OH)D and the risk of wither cutaneous melanoma or non melanoma skin cancer. Studies had to be case-control, nested case control, cohort of randomised clinical trial design, reporting a measure of relative risk with 95%CI or another measure of statistical uncertainty. Including a measure of tumour thickness. *Exclusion:* Ecological studies, case reports, reviews and editorials were not considered eligible Outcome measure Cutaneous melanoma and non melanoma skin cancer.	Highest versus lowest quantile of 25(OH)D Basal cell carcinoma: 4 studies, 1221 cases RR 1.82 (95%CI 1.38, 2.40) Squamous cell carcinoma: 3studies, 328 cases RR 1.68 (95%CI 0.44, 6.39) Non melanoma skin cancer: 2 studies, 768 cases RR 1.64 (95%CI 1.02, 2.65)	Higher serum 25(OH)D concentration was associated with a significant increase in risk in basal cell skin cancer and non melanoma skin cancer.

Table 32 - Prospective studies of circulating vitamin 25-OHD and cancer risk

Reference/ country	Population description	Follow up	Mean 25(OH)D	Results/ comments
Colorectal cancer				
Woolcott et al. (2010)	Adults from a Multiethnic Cohort including men and women of Japanese, Latino, African American, White, and Native Hawaiian ancestry. Cases – 229 (63.8% male) Controls – 434 (64.1% male) Mean age 69 years	1.7 years	Cases – 23.2ng/ml (10.1) Controls – 25.0ng/ml (9.9) Q1 <16.8ng/ml Cases – 67/Controls 87 Q2 16.8<22.2ng/ml Cases – 42/Controls – 86 Q3 22.2<26.3ng/ml Cases – 38/Controls – 88 Q4 26.3<32.8ng/ml Cases – 43/Controls – 87 Q5 ≥32.8ng/ml Cases – 39/Controls - 86	Q1 (ref) Q2 OR 0.63 (95%CI 0.37, 1.08) Q3 OR 0.54 (95%CI 0.32, 0.93) Q4 OR 0.62 (95%CI 0.36, 1.07) Q5 OR 0.60 (95%CI 0.33, 1.07) OR per doubling of 25(OH)D 0.68 (95%CI 0.51, 0.92) p=0.01 Increasing risk of colorectal cancer with low 25(OH)D concentrations.
Weinstein et al. (2011) Finland	Adults taking part in the ATBC study Cases- 428 Controls - 428	6.1 years (median)	Colon cancer cases – 32.4nmol/L (22.5-49.3) Controls – 29.6nmol/L (20.5-45.7) Rectum cancer cases – 34.6nmol/L (21.3-50.9) Controls – 31.2nmol/L (22.1-45.6)	Colorectal cancer <25nmol/L Cases – 143; Controls - 155 0.68 (95%CI 0.45, 1.03) 25<37.5nmol/L Cases – 105; Controls – 105 0.78 (95%CI 0.51, 1.20) 37.5<50nmol/L Cases – 73; Controls – 77 0.78 (95%CI 0.49, 1.25) 50<75nmol/L Cases – 85; Controls – 72 1.00 reference ≥75nmol/L Cases – 22; Controls – 19 1.0 (95%CI 0.49, 2.03) Non significant higher risk for participants in the highest category of 25(OH)D

Lee et al. (2011) USA	Men taking part in the Physicians' Health study Cases – 229 Controls - 389	8.9 years (median)	Median Q1 - 15.7ng/ml Cases – 57 Controls – 96 Q2 – 22.3ng/ml Cases – 41 Controls – 97 Q3 – 26.7ng/ml Cases – 74 Controls – 99 Q4 – 37.9ng/ml Cases – 57 Controls - 97	Colorectal cancer Q1 1.00 ref Q2 0.71 (95%CI 0.42, 1.21) Q3 1.24 (95%CI 0.76, 2.04) Q4 1.08 (95%CI 0.62, 1.87) P=0.67 Colon cancer Q1 1.00 ref Q2 0.95 (95%CI 0.52, 1.74) Q3 1.34 (95%CI 0.75, 2.39) Q4 1.38 (95%CI 0.73, 2.64) P=0.35 Rectal cancer Q1 1.00 ref Q2 0.53 (95%CI 0.18, 1.60) Q3 0.42 (95%CI 0.13, 1.40) Q4 0.45 (95%CI 0.14, 1.46) P=0.05 No significant association with overall colorectal cancer risk. When colon & rectal cancer examined separately inverse association suggested for rectal cancer.
Neuhouser et al. (2012) USA	Postmenopausal women Mean age: 65.1 years (6.8) Cases – 310 Controls - 310		Q1 ≥64.5nmol/L – 130 Q2 43.6<64.5nmol/L – 162 Q3 32.7<43.6nmol/L – 147 Q4 <32.7nmol/L - 181	Q1 1.00 ref Q2 2.76 (95%CI 1.30, 5.89) Q3 1.51 (95%CI 0.72, 3.14) Q4 4.45 (95%CI 1.96, 10.10) P=0.003 Women with low 25(OH)D concentration versus high 25(OH)D concentration had a 4 fold increased risk of colorectal cancer.

Weinstein et al (2014)	Participants taking part in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) cohort Age 55-74 years Cases – 476 Controls - 476	5.6 years (median) 0.3-11.4 years (interquartile)	Cases – 52.3nmol/L (39.6-64.8) Controls – 56.5nmol/L (41.2-71.1)	Season-specific quintiles for December–May were Q1: ≤ 33.6, Q2:>33.6 and ≤44.6, Q3:>44.6 and ≤ 55.7, Q4:>55.7 and ≤ 68.0, Q5:>68.0 nmol/L; and for June-November were Q1: ≤ 44.1, Q2: >44.1 and ≤ 57.3, Q3:>57.3 and ≤ 66.4, Q4:>66.4 and ≤ 78.2, Q5:>78.2 nmol/L BMI adjusted OR Q1 109 cases, 96 controls Ref Q2 119 cases, 95 controls 1.07 (95%CI 0.73, 1.56) Q3 97 cases, 96 controls 0.84 (95%CI 0.56, 1.25) (BMI adjusted OR) Q4 82 cases, 93 controls 0.76 (95%CI 0.50, 1.14) (BMI adjusted OR) Q5 69 cases, 94 controls 0.60 (0.38, 0.94) (BMI adjusted OR) P=0.01 Multivariate adjusted OR Q1 Ref Q2 1.05 (95%CI 0.70, 1.16) Q3 0.89 (95%CI 0.58, 1.36) Q4 0.80 (95%CI 0.52, 1.25) Q5 0.59 (95%CI 0.36, 0.95) P=0.02 Circulating 25(OH)D was inversely associated with colorectal cancer.
Breast cancer				
Kim et al 2014 Los Angeles & Hawaii, US	36,458 postmenopausal women in the multiethnic cohort study. Age 45–75 years Ethnicity: white, African-American, Native Hawaiian, Japanese and Latino. Cases – 707 Controls - 707	3.1 years (mean)	White Cases – 34.9ng/ml (10.2) Controls – 37.4ng/ml (9.7) African American Cases – 25.7ng/ml (12.1) Controls – 26.4ng/ml (11.3) Native Hawaiian Cases – 32.6ng/ml (8.7) Controls – 33.4ng/ml (12.2) Japanese Cases – 32.7ng/ml (9.3) Controls – 32.6ng/ml (10.2) Latino Cases – 27.7ng/ml (9.4) Controls – 27.1ng/ml (9.4)	Per 25nmol/L increase White subjects OR 0.66 (95%CI 0.48, 0.90) African-American subjects OR 1.08 (95%CI 0.79, 1.47) Native Hawaiian subjects OR 0.79 (95%CI 0.52, 1.20) Japanese subjects OR 1.04 (95%CI 0.84, 1.28) Latino subjects OR 1.17 (95%CI 0.84, 1.64) Overall P=0.086 White subjects vs other subjects p=0.051 A 25nmol/L increase in 25(OH)D was associated with a reduced risk of breast cancer among white subjects.

Prostate cancer				
Meyer et al (2013) Norway	Males who participated in population based health studies between 1981 and 1991. Cases – 2106 Controls – 2106 Mean age: 48.2 years	16.1 years (median)	Winter & spring combined Cases – 55.8nmol/L (±19.2) Controls – 56.0nmol/L (±21.3) Summer & autumn combined Cases – 72.2nmol/L (±22.1) Controls – 68.9nmol/L (±22.1)	All <30nmol/L 0.82 (95%CI 0.58, 1.15) 30-49nmol/L 1.02 (95%CI 0.86, 1.20) 50-69nmol/L 1.00 ref 70-89nmol/L 1.25 (95%CI 1.05, 1.47) ≥90nmol/L 1.22 (95%CI 0.97, 1.53) Per 30nmol/L increase 1.15 (95%CI 1.04, 1.27) Winter & Spring / Summer & autumn <30nmol/L 0.78 (95%CI 0.51, 1.20) / 1.00 (95%CI 0.47, 2.17) 30-49nmol/L 1.08 (95%CI 0.85, 1.38) / 0.86 (95%CI 0.65, 1.14) 50-69nmol/L 1.00 ref 70-89nmol/L 1.15 (95%CI 0.86, 1.53) / 1.33 (95%CI 1.05, 1.70) ≥90nmol/L 0.79 (95%CI 0.50, 1.26) / 1.50 (95%CI 1.10, 2.05) Per 30 increase 1.00 (95%CI 0.85, 1.17) / 1.27 (95%CI 1.08, 1.45) For all cases and controls there was a positive association between 25(OH)D and risk of prostate cancer. No correlation with 25(OH)D collected in winter and spring. Positive association with 25(OH)D collected in summer and autumn and men with a 25(OH)D concentration ≥90nmol/L had a 50% increased risk of prostate cancer compared to men with a 25(OH)D concentration between 50 and 69nmol/L.
Albanes et al 2011 Finland	Men in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study Cases – 1000 Controls - 1000 Age: 50-69 years	5-8 years (median 6.1 years)	Cases – 34.5nmol/L (22.7-50) Controls – 33.6nmol/L (21.4-49.1)	Season specific *Q1: ≤16.3nmol/L (less sunny month) ≤25.9nmo/L (for sunnier months)* OR 1.00 Ref *Q2: >16.3 and ≤23.8nmol/L (less sunny month) >25.9 and ≤ 35.7nmol/L (sunnier months)* OR 1.29 (95%CI 0.95, 1.74) *Q3: >23.8 and ≤33.3nmol/L (less sunny months) >35.7 and ≤48.3nmol/L* OR 1.34 (95%CI 1.00, 1.80) *Q4: >33.3 and ≥45.6nmol/L (less sunny months) >48.3 and ≤59.9nmol/L (sunnier months)* OR 1.26 (95%CI 0.93, 1.72) Q5 >45.6nmol/L (less sunnier months) >59.9nmol/L (sunnier months) OR 1.56 (95%CI 1.15, 2.12) P=0.01 .
Brandstedt et al 2012 Finland	Men with prostate cancer in the MalmÖ Diet and Cancer Study cohort. Cases – 443 Controls – 443 Age: 69.3 years	7.6 years (0.1-15.5 years)	Cases – 87.7nmol/L (26.4) (20-204) Controls – 86.4nmol/L (27.3) (18-205)	Q1 ≤68nmol/L 206 cases & 242 controls OR 1.00 Ref Q2 69-84nmol/L 237 cases & 232 controls OR 1.25 (95%CI 0.95, 1.65) Q3 85-102nmol/L 245 cases & 226 controls OR 1.37 (95%CI 1.03, 1.82) Q4≥103nmol/L 230 cases & 224 controls

				OR 1.34 (95%CI 0.99, 1.82) P=0.048 Weak trend for increasing prostate cancer risk with rising25(IH)D conc.
Schenk et al 2014 US	Men in the Prostate Cancer Prevention trial. Cases – 1695 Controls – 1682 Age: 55 years plus	1 year	Lowest quartile <44.7nmol/L Highest quartile ≥71.2nmol/L	Q1 Ref Q2 0.97 (95%CI 0.79, 1.18) Q3 1.07 (95%CI 0.87, 1.30) Q4 1.10 (95%CI 0.90, 1.35) No association between serum 25(OH)D and total cancer risk.
Kristal et al 2014 US	Men in the Selenium and Vitamin E Cancer Prevention Trial Cases – 1731 Controls – 3203 Mean age Cases – 63.5 years (±6.1) Controls – 63.3 years (±6.5)		Mean 69.2nmol/L (±28.8) <37.5nmol/L 12.2% 37.5 - <50nmol/L 14.7%	<37.5nmol/L HR 1.00 Ref 37.5 - <50nmol/L 1.08 (95%CI 0.83, 1.41) p=0.57 50 - <75nmol/L 0.89 (95%CI 0.70, 1.12) p=0.33 ≥75nmol/L 0.98 (95%CI 0.78, 1.24) p=0.9 No significant association.
Shui et al 2012	Men in the Health Professionals Follow up Study Cases – 1260 Controls – 1331 Age: 40-75 years	5.2 years (2.9-7.5) (median)	Not reported	Lethal prostate cancer Q1: OR 1.0 Ref Q2: OR 0.77 (95%CI 0.47, 1.28) Q3: OR 0.50 (95%CI 0.28, 0.88) Q4: OR 0.43 (95%CI 0.24, 0.76) P=0.001 Overall prostate cancer Q1: OR 1.0 Ref Q2: OR 0.93 995%CI 0.75, 1.17) Q3: OR 0.98 (95%CI 0.78, 1.22) Q4: OR 1.05 (95%CI 0.84, 1.32) P=0.57 57% reduction in risk of lethal prostate cancer (highest vs lowest quartile). No significant association between 25(OH)D and overall prostate cancer.

Oesophagus and stomach				
Abnet et al 2010	Participants pooled from 8 cohort studies (Cohort Consortium Vitamin D Pooling Project of Rarer Cancers). Cases – 1065 Controls -1066 Median age: Cases – 61 years (55-67) Controls – 61 years (55-66)	5.3 years (2.4-9.1) (median)	Cases – 39.4nmol/L (26.3-56.1) Controls – 39.3nmol/L (26.1-56.3) (median)	<25nmol/L: OR 0.90 (95%CI 0.65, 1.24) 25-<37.5nmol/L: OR 1.03 (95%CI 0.76, 1.39) 37.5-<50nmol/L: OR 0.92 (95%CI 0.69, 1.23) 50-<75nmol/L: OR 1.0 Ref 75-<100nmol/L: OR 1.17 (95CI 0.79, 1.75) ≥100nmol/L: OR 0.81 (95%CI 0.39, 1.69) P=0.54 No association between 25(OH)D concentration and risk of upper GI cancer.
Larynx and oropharynx				
Arem et al 2011 Finland	Male smokers taking part in the Alpha-Tocopherol Beta Carotene study. Age: 50-69 years Cases – 340 (134 oral cavity, 48 pharynx, 158 larynx) Controls - 340	20 years.	Cases – 31nmol/L (21-47) Controls – 32nmol/L (21-48)	All cancer Q1 <25nmol/L: OR 0.96 (95%CI 0.58, 1.59) Q2 25 - <37.5nmol/L: OR 1.11 (95%CI 0.65, 1.88) Q3 37.5 - <50.0nmol/L: Ref Q4 ≥75nmol/L: 1.35 (95%CI 0.53, 3.43) P=0.65 No association.
Lung cancer				
Kilkkinen et al 2008 Finland	Cohort study Cases - 122	24 years	42.9nmol/L (±19.6) Men – 45.2nmol/L (±20.4) Women – 41nmol/L (±18.7)	1st tertile (M 5-35nmol/L; F 4-30nmol/L): RR 1.0 Ref 2nd tertile (M 35-51nmol/L; F 31-46nmool/L): RR 0.96 (95%CI 0.63, 1.45) 3rd tertile (M 52-180nmol/L; F 47-51nmol/L): RR 0.72 (95%CI 0.43, 1.19): No significant association.
Weinstein et al 2011 Finland	Participants in the ATBC study. Cases – 500 Controls – 500 Mean age: 59 years (55-62)	20 years	Cases – 33.6nmol/L (20.7-50.2) Controls – 35nmol/L (21.5-50.5)	Q1 95 cases & 101 controls: OR 1.00 Ref Q2 120 cases & 100 controls: OR 1.28 (95%CI 0.83, 1.99) Q3 108 cases & 100 controls: OR 1.20 (95%CI 0.77, 1.86) Q4 71 cases & 100 controls: OR 0.83 (95%CI 0.52, 1.35) Q5 106 cases & 99 controls: OR 1.08 (95%CI 0.67, 1.75) P=0.58 Serum 25(OH)D was not associated with lung cancer risk.
Endometrium cancer				
Zeleniuch-Jacquotte et al (2010)	Women from 7 cohorts (Cohort Consortium Vitamin D Pooling Project of Rarer Cancers). Cases – 830 Controls – 992 Mean age: Cases – 58 years (50-65) Controls – 58 years (50-64)	1.7-10.7 years depending on each cohort (median)	Cases – 49.4nmol/L (34.6-66.4) Controls – 50.8nmol/L (36.7-67.1)	<25nmol/L 93 cases & 88 controls: OR 1.02 (95%CI 0.68, 1.53) 25-<37.5nmol/L 162 cases & 170 controls: OR 0.91 (95%CI 0.67, 1.24) 37.5-<50nmol/L 163 cases & 224 controls: OR 0.79 995%CI 0.60, 1.05) 50-<75nmol/L 293 cases & 349 controls: OR 1.0 Ref 75-<100nmol/L 94 cases & 126 controls: OR 1.00 (95%CI 0.71, 1.42) ≥100nmol/L: OR 0.85 (95%CI 0.47, 1.53) P=0.81 No association between 25(OH)D concentrations and endometrium cancer.

Kidney cancer				
Gallicchio et al 2010	Participants pooled from 8 cohort studies (Cohort Consortium Vitamin D Pooling Project of Rarer Cancers). Cases – 775 Controls – 775 Median age: 60 years (54-66) 74.5 % males	Median follow up: 5.5 years (2.7-9.9)	Cases – 44.4nmol/L (30.7-62.9) Controls – 45.4nmol/L (30.2-62.5) (median)	<25nmol/L 119 cases & 136 controls: OR 0.94 995%CI 0.64, 1.37) 25-<37.5nmol/L 164 cases & 152 controls: OR 1.18 (95%CI 0.84, 1.67) 37.5-<50nmol/L 173 cases & 144 controls: OR 1.18 (95%CI 0.85, 1.62) 50-<75nmol/L 219 cases & 240 controls: OR 1.0 Ref 75-<100nmol/L 80 cases & 75 controls: OR 1.19 (95%CI 0.78, 1.83) ≥100nmol/L 20 cases & 28 controls: OR 0.92 (95%CI 0.44, 1.92) P=0.86 No association between 25(OH)D concentration and kidney cancer.
Mondul et al 2014 Finland	Participants from the ATBC study. Cases – 262 Controls – 262 Median age: 57 years (54-61)		*Q1 <19nmol/L (winter) <29nmol/L (summer)* 68 cases/73 controls *Q2 19-<29nmol/L (winter) 29-<43nmol/L (summer)* 64 cases/67 controls *Q3 29-<44nmol/L (winter) 43-<57nmol/L (summer)* 74 cases/74 controls *Q4 ≥44nmol/L (winter) ≥57nmol/L (summer)* 75 cases/67 controls	Q1 OR 1.00 Ref Q2 OR 0.99 (95%CI 0.60, 1.63) Q3 OR 1.17 (95%CI 0.71, 0.91) Q4 OR 1.45 995%CI 0.86, 2.44) P=01.8 No association between 25(OH)D and kidney cancer.
Non-Hodgkin lymphoma				
Purdue et al 2010	Participants pooled from 10 cohort studies (Cohort Consortium Vitamin D Pooling Project of Rarer Cancers). Cases – 1353 Controls – 1778 Median age: Cases – 62 years (56-68) Controls – 61 years (55-67)	Median follow up 5.2 years (2.5-8.7)	Cases - 55.7nmol/L (40.6-70.1) Controls – 53.5nmol/L (38.8-68.8)	<25nmol/L 100 cases, 105 controls: OR 1.08 (0.78, 1.50) 25-<37.5nmol/L 154 cases, 203 controls:OR 0.92 95%CI 0.71, 1.19) 37.5-<50nmol/L 261 cases, 319 controls: OR 0.98 (95%CI 0.79, 1.21) 50-<75nmol/L 505 cases, 567 controls: OR 1.0 Ref 75-<100nmol/L 204 cases, 198 controls: OR 1.15 (95%CI 0.91, 1.46) ≥100nmol/L 49 cases, 64 controls: OR 0.86 (95%CI 0.57, 1.27) P=0.68 No association between 25(OH)D concentration and non-Hodgkin lymphoma.
Hepatocellular cancer				
Fedirko et al 2014	Participants in the European Prospective Investigation into Cancer and Nutrition (EPIC) Cases – 138 Controls - 138	6 years (3.4)	Cases – 41.7nmol/L (16.9-82.3) Controls – 49.9nmol/L (24.8-90.9) (mean (5^{th} -95^{th} percentile)	Tertile 1: 33.5nmol/L (7.7) (mean): IRR 1.0 Ref Tertile 2: 51.3nmol/L (4.4): IRR 0.53 (95%CI 0.27, 1.04) Tertile 3: 73.6nmol/L (13.7): IRR 0.51 (95%CI 0.26, 0.99) P=0.036 <50nmol/L: IRR 1.82 (95%CI 1.02, 3.26) 50-<75nmol/L: IRR 1.00 Ref >75nmol/L: IRR 0.73 (95%CI 0.25, 2.13) P=0.016 Higher 25(OH)D associated with a lower risk of liver cancer.

Wang et al (2013) China	Participants from the Linxian Nutrition Intervention Trial Cases – 226 liver cancer Controls – 1063 Median age: Cases – 55 years (49-61) Controls – 55 years (50-61)	Over 22 years	Cases – 20nmol/L (14-28.6) Controls – 20.1nmol/L (13.7-30.3) (median)	Q1 <11.17nmol/L (F) & <18.14nmol/L (M): OR 1.00 Ref Q2 ≥11.7- <14.86nmol/L (F) & ≥18.4- <25.33nmol/L (M): OR 0.91 (95%CI 0.60-1.37) Q3 ≥14.86- <21.8nmol/L F) & ≥25.33-<38.84nmol/L (M): OR 0.87 (95%CI 0.57, 1.31) Q4 ≥21.8nmol/L (F) & ≥38.84nmol/L (M): OR 0.74 (95%CI 0.47, 1.18) P=0.2 No significant association between serum 25(OH)D and the risk of liver cancer incidence.
Bladder cancer				
Mondul et al 2010 Finland	Participants in the ATBC study. Cases – 250 Controls – 250 100% male Median age: Cases – 59 years (55-63) Controls – 59 years (56-63)	20 years	*<25nmol/L* 83 cases & 73 controls *25-<37.5nmol/L* 61 cases & 52 controls *37.5-<50nmol/L* 54 cases & 46 controls *≥50nmol/L* 52 cases & 79 controls	<25nmol/L: OR 1.73 (95%CI 1.03, 2.91) 25-<37.5nmol/L: OR 1.81 (95%CI 1.05, 3.14) 37.5-<50nmol/L: OR 1.76 (95%CI 1.02, 3.02) ≥50nmol/L: OR 1.0 Ref P=0.04 Men with a 25(OH)D concentration below 50nmol/L were at nearly twice the risk of bladder cancer compared to men with a 25(OH)D concentration ≥50nmol/L.
Mondul et al 2012 US	Participants form the PLCO study. Cases – 375 Controls – 375 Median age: Cases – 64 years (60-68) Controls – 64 years (61-67) 80.8% male	13 years	Cases – 52.4nmol/L (39.6-65.8) Controls – 53.6nmol/L (39.5-68.1)	<25nmol/L: OR 0.74 (95%CI 0.29, 1.87) 25-<37.5nmol/L: OR 0.72 (95%CI 0.43, 1.23) 37.5-<50nmol/L: OR 1.17 (95%CI 0.76, 1.80) 50-<75nmol/L: OR 1.0 Ref ≥75nmol/L: OR 0.85 (95%CI 0.53, 1.38) P=0.99 No significant association between 25(OH)D and bladder cancer.
Melanoma				
Major et al (2012) Finland	Participants in the ATBC study. Cases – 92 Controls – 276 Median age: Cases – 57.5 years (53.5-61) Controls – 57 years (53.5-61)	Cases – 8.9 years Controls – 18.2 years (median)	Cases – 33.1nmo/L (21.9-51.6) Controls – 31.8nmol/L (20.9-48.5) (median)	<25nmol/L: OR 1.0 Ref 25-27.49nmol/L: OR 1.04 (95%CI 0.52, 2.12) 37.5-49.99nmol/L: OR 0.60 (95%CI 0.25, 1.44) ≥50nmol/L: OR 1.32 (95%CI 0.64, 2.72) P=0.51 Overall. no association between serum 25(OH)D &melanoma risk; non- significant higher risk in people with 25(OH)D ≥50nmol/L vs <25nmol/L.
Afzal et al 2013 Denmark	Participants in the Copenhagen City Heart Study. n=10,060 78 cases of melanoma	28 years	Whole population - 41nmol/L Melanoma – 51nmol/L	≥50nmol/L vs <25nmol/L: HR 4.7 (95%CI 0.96, 23.3) $>67^{th}$ vs $≥34^{th}$: HR 6.31 (95%CI 1.38, 28.8) Per 10nmol/L increase in 25(OH)D: HR 1.45 (95%CI 1.22, 1.73) 10% increase in seasonally adjusted percentile of 25(OH)D HR 1.27 (95%CI 1.05, 1.53) Increasing 25(OH)D associated with increased risk of melanoma skin cancer.

Van der Pols et al 2013 Australia	1191 adults in an Australian subtropical community. 300 cases of basal cell carcinoma 176 cases of squamous cell carcinoma 17 cases of melanoma Mean age: 54 years	11 years	<50nmol/L 22% 50-75nmol/L 47% >75nmol/L 31%	Basal cell carcinoma <75nmol/L 193 cases & 828 controls: OR 1.00 Ref ≥75nmol/L 107 cases & 363 controls: OR 1.51 (95%CI 1.10, 2.07) P=0.01 Squamous cell carcinoma <75nmol/L 132 cases & 828 controls: OR 1.00 Ref ≥75nmol/L 44 cases & 363 controls: OR 0.67 (95%CI 0.44, 1.03) P=0.07 Melanoma <75nmol/L 9 cases & 828 controls: OR 1.00 Ref ≥75nmol/L 8 cases & 363 controls: OR 2.71 (95%CI 0.98, 7.48) P=0.05 Participants with 25(OH)D > 75nmol/L more likely to develop basal cell carcinoma and melanoma compared to those < 75nmol/L.
Pancreatic cancer				
Stolzenberg-Solomon et al (2010)	Participants pooled from 8 cohort studies (Cohort Consortium Vitamin D Pooling Project of Rarer Cancers). Cases – 952/Controls – 1333 Median age: Cases–62 y (56-68)/Controls–62 y (57-67)	6.5 years (median)	Cases – 49.3nmol/L (2.0-156) Controls – 50.8nmol/L (2.6-127.2) (median)	<25nmol/L: OR 1.0 Ref 25- <37.5nmol/L: OR 1.04 (95%CI 0.74, 1.44) 37.5- <50nmol/L: OR 1.10 (95%CI 0.79, 1.55) 50- <75nmol/L: OR 1.06 (95%CI 0.76, 1.48) 75-<100nmol/L: OR 1.08 (95%CI 0.73, 1.59) ≥100nmol/L: OR 2.24 (95%CI 1.22, 4.12) P=0.14 Significant increase in risk with higher compared to lower 25(OH)D

Table 33 - Trials of vitamin D and cancer risk

Study/year/ country	Study population	Intervention	Baseline 25(OH)D	Post intervention 25(OH)D	Cancer outcome	Results Cases -Intervention/placebo	Comments
Trivedi et al 2003 Suffolk, UK	n=2686 Men - 2037 Women – 649 Age: 65-85 years Recruited from the British doctors register and a general practice register.	1. 2500µg/4 months (equiv 21 µg/d) 2. Placebo Duration: 5 years	Not reported	Not reported	Colon cancer mortality	1. 7 cases 2. 11 cases HR 0.62 (95%CI 0.24, 1.60) P=0.33	No association.
					All cancer mortality	1. 63 cases 2. 72 cases HR 0.86 (95%CI 0.61, 1.20)	No association
Lappe et al 2007 Nebraska, USA	Healthy postmenopausal women n= 734 Age: >55 years	1. 27.5 µg/d D3 + 1450 mg/d Ca 2. 1400-1500mg/d Ca 3. Placebo Duration: 4 years	1. 71.8nmol/L (±20) 2. 71.6nmol/L (±20.5) 3. 72.1nmol/L (±20.7)	At 12 months: 1. 96nmol/L (±21.4) 2. 71nmol/L (±20.3) 3. 71.1nmol/L (±19.8)	All cancers	1. 13 cases 2. 17 cases 3. 20 cases 0.40 (0.20-0.82)	There was a reduced risk of cancer in the vitamin D and calcium group and calcium only group.
Wactawski-Wende et al 2006 Women's Health Initiative, USA	Healthy postmenopausal women n=36,282	1.10 µg D3 with 1000mg/d Ca 2. Placebo Duration: 7 years	Not reported	Not reported	Colorectal	1. 168 cases 2. 154 cases 1.08 (0.86-1.34) P=0.51	Vitamin D and calcium supplementation for 7 years had no effect on the incidence of colorectal cancer in postmenopausal women.
Avenell et al 2012 UK RECORD	Participants recruited from fracture clinics n=5292 Age: >70 years	1. 20 µg D3/d 2. 1000mg/d Ca 3. 20 µg D3 + 1000 mg/d Ca 4. Placebo Duration: 24-62 m intervention & 3 years post intervention	Not reported	Not reported	All cancers	1. 338 cases (with vitamin D or calcium) 4. 315 cases (without vitamin D or calcium) HR 1.07 (95%CI 0.92, 1.25) P=0.376	No effect on cancer incidence.

Cardiovascular disease

Table 34- Meta-analyses

Study	Methods	Results	Conclusions
Grandini et al (2010) Vitamin D and cardiovascular disease: systematic review and meta-analysis of prospective studies	Selection criteria: *Inclusion*: Cohort or nested case–control studies reporting hazard ratios, relative risks or odds ratios for the association of initial 25-OH-D levels with incident cardiovascular events or cardiovascular mortality either in a general (initially healthy) human population or in a population with pre-existing CHD were eligible for inclusion. Studies investigating incident fatal or non-fatal myocardial infarction (MI), acute coronary syndrome, CHD or combined outcomes of cardiovascular and cerebrovascular diseases (stroke) were also included. *Exclusion:* Articles not in English or if the study population was selected according to presence of a disease other than CVD. Studies where exposure and disease status had been determined simultaneously were excluded. Studies analysing clinical outcomes of peripheral arterial disease, congestive heart failure, atherosclerosis or stroke were only eligible if those outcomes were analysed in combination with CHD endpoints. Outcome measure Cardiovascular disease incidence and mortality.	25(OH)D and CVD incidence: 3 cohort studies and 1 nested case control study; mean age 59-79 years; follow up 5-10 years RR 1.54 (95%CI 1.22, 1.95) p=0.47 CVD mortality: 5 cohort studies; mean age 45-75 years, follow up 6.2-27.1 years RR 1.83 (95%CI 1.19, 2.79) P=0.006	There was an association between baseline 25(OH)D in the lowest compared to the highest category with cardiovascular events. There was a significant association between low 25(OH)D concentrations and cardiovascular mortality
Wang et al 2010 Systematic review: Vitamin D and calcium supplementation in prevention of cardiovascular events	Selection criteria: *Inclusion*: prospective studies and randomised controlled trials that examined vitamin D supplementation, calcium supplementation or both and subsequent cardiovascular events. *Exclusion*: ecological, cross-sectional and retrospective case-control studies. Case reports, studies of children and adolescents and studies that did not assess the use of vitamin D supplements, calcium supplements or their combination. Review articles, editorials, letters to editors, studies lacking a comparison between participants who received vitamin D supplements, calcium supplements or a combination and non-recipients and studies that did not ascertain CVD events. Outcome measure Cardiovascular events	RCTs: Vitamin D alone: 2 RCTs, 25µg/d (1000IU) to 2500µg/ 4 months (100,000IU) RR 0.90 (95%CI 0.77, 1.05) Vitamin D & calcium: 2 RCTs, 10µg/d (400IU) to 20µg/d (800IU) RR 1.04 (95%CI 0.92, 1.18)	Slight significant reduction in cardiovascular risk with vitamin D supplementation vs palcebo. No significant reduction in CVD risk with vitamin D and calcium supplements vs placebo. (secondary analysis)

Study	Methods	Results	Conclusions
Bolland et al 2011 Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis	Selection criteria: *Inclusion:* not reported *Exclusion:* not reported Outcome measure Cardiovascular events	Calcium and vitamin D supplements and cardiovascular events: 3 trials Myocardial infarction: RR 1.21 (95%CI 1.01, 1.44) p=0.04 Stroke: RR 1.20 (95%CI 1.00, 1.43) p=0.05 Myocardial infarction or stroke: RR 1.16 (95%CI 1.02, 1.32) p=0.02	Calcium and vitamin D supplementation increased the risk of myocardial infarction and stroke.
Wang et al 2012 Circulating 25-hydroxy-vitamin D and risk of cardiovascular disease: a meta-analysis of prospective studies	Selection criteria: *Inclusion:* prospective studies that examined the association between circulating 25(OH)D at baseline and risk of CVD events. *Exclusion:* Ecological, cross-sectional or retrospective case control studies. Review articles, commentaries, editorials or case reports. Studies that did not measure 25(OH)D or ascertain major clinical CVD events. Studies that did not compare CVD event rates between different 25(OH)D concentrations and studies of participants selected by confirmed medical conditions. Outcome measure Cardiovascular disease outcomes.	22 cohort studies and 2 nested case-control studies, 6123 CVD cases from 65994 participants. Total CVD – lowest vs highest 25(OH)D RR 1.52 (95%CI 1.30, 1.77) p=0.57 Per 25nmol/L decrease in 25(OH)D RR 1.18 (95%CI 1.07, 1.29) CVD mortality RR 1.42 (95%CI 1.19, 1.71) CHD RR 1.38 (95%CI 1.21, 1.57) Stroke RR 1.64 (95%CI 1.27, 2.10)	A significant association between lower serum 25(OH)D concentrations and increased risk for total CVD and CHD.
Ford et al 2014 Cardiovascular disease and vitamin D supplementation: trial analysis, systematic review, and meta-analysis	Selection criteria: *Inclusion:* RCTs with subjects ≥60years (mean or median) and ≥1 year follow up. Any vitamin D or vitamin D analog intervention were included. Coadministration with other medication e.g. calcium were included provided that the comparator group received the same medication. *Exclusion:* Studies that assessed vitamin D supplementation in participants selected solely on the basis of renal impairment, steroid induced osteoporosis, or psoriasis. Outcome measure Cardiovascular disease outcomes.	21 RCTs (n=13,033; mean/median age ≥ 60 years; ≥ 1 year follow-up) Cardiac failure HR 0.82 (95%CI 0.58, 1.15) MI 0.96 (95%CI 0.83, 1.10) Stroke HR 1.07 (95%CI 0.91, 1.29)	Vitamin D supplementation may be protective for heart failure in older adults, however it does not appear to protect against MI or stroke.

Hypertension

Table 35 - Meta-analyses

Study	Methods	Results	Conclusions
Burgaz et al 2011 Blood 25-hydroxyvitamin D concentration and hypertension: a meta-analysis	Selection criteria: *Inclusion:* Cohort, case-control or cross-sectional design. The exposure was plasma or serum 25(OH)D concentrations. Studies of adults aged >18 years and results reported as RR or OR with 95%CI. *Exclusion:* Outcome measure Hypertension	18 studies (4 prospective and 14 cross-sectional) Highest vs lowest 25(OH)D concentration OR 0.73 (95%CI 0.63, 0.84) p=0.007 For a 40nmol/L increase in 25(OH)D OR 0.84 (95%CI 0.78, 0.90) p=0.000	25(OH)D concentration inversely associated with hypertension.
Witham et al 2009 Effect of vitamin D on blood pressure: a systematic review and meta-analysis	Selection criteria: *Inclusion:* randomised controlled design, comparison of regimen based on vitamin D with placebo. Included studies that used ultraviolet light to produce an increase in vitamin D level. *Exclusion:* Not reported Outcome measure Blood pressure reduction or cardiac risk factor modification	11 studies Systolic blood pressure -3.6mmHg (95%CI -8.0, 0.7) Diastolic blood pressure -3.1mmHg (95%CI -5.5, -0.6)	Small significant reduction in diastolic blood pressure.
Wu et al 2010 Effects of vitamin D supplementation blood pressure	Selection criteria: *Inclusion:* RCTs studying oral vitamin D supplementation in normotensive or hypertensive individuals. Require baseline and follow up blood pressure from baseline to the end of follow up. *Exclusion:* uncontrolled trials, observational and animal studies. Patients with kidney diseases, hypercalcemia, diabetes, pregnant women and children. Subjects with impaired glucose tolerance. Outcome measure Change in participants blood pressure.	4 double blind RCTs (n=429); mean age 64 years; 73% women Systolic blood pressure -2.44mmHg (95%CI -4.86, -0.02) Diastolic blood pressure -0.02mmHg (95%CI -4.04, 4.01)	Ssignificant reduction in systolic blood pressure.

Study	Methods	Results	Conclusions
Pittas et al 2010 Vitamin D and cardiometabolic outcomes: a systematic review	Selection criteria: *Inclusion:* Generally healthy populations, combined terms for vitamin D, hypertension and CVD. English language only. Nested case control studies where data on vitamin D status were collected prior to outcome assessment *Exclusion:* Cross-sectional and retrospective cohort studies, standard case control studies and short term (<1month) randomised controlled trials. Studies in children, pregnant women, and patients with conditions that affect vitamin D metabolism (e.g. chronic kidney disease, hyperparathyroidism) and trials that used a vitamin D preparation other than D2 and D3. Outcome measure Incident hypertension, incident CVD, and change in blood pressure (trials only).	Cohort studies: 3 studies on 4 cohorts (32,181 participants), follow up 7-10 years. 1 study assessed vitamin D status by self reported vitamin D intake and 2 studies measured 25(OH)D. Meta-analysis of 3 cohorts that assessed 25(OH)D concentration Lowest (<37-51nmol/L) versus highest (>75-81nmol/L) RR 1.76 (95%CI 1.27, 2.44) RCTs: 9 trials – 400-8571IU/d, 37,162 participants. Systolic blood pressure Weighted mean difference -1.9mmHg (95%CI -4.2, 0.4) Diastolic blood pressure Weighted mean difference -0.1mm Hg (95%CI -0.7, 0.5) .	Cohort studies There was a statistically significant association comparing the lowest vs the highest 25(OH)D concentration and incident hypertension. RCTs No statistically significant effect of vitamin D supplementation vs placebo on systolic blood pressure or diastolic blood pressure
Kunutsor et al 2014 Vitamin D and high blood pressure: causal association or epiphenomenon?	Selection criteria: *Inclusion:* RCTs that studied the effects of oral vitamin D supplementation alone. *Exclusion:* Studies with calcitriol or one of its analogues as the intervention Outcome measure The difference in office or ambulatory systolic and diastolic blood pressure.	Systolic blood pressure: 16 trials, 800IU to 8571IU per day -0.94mmHg (95%CI -2.98, 1.10) Diastolic blood pressure: 15 trials, 800IU to 8571IU per day -0.52mmHg (95%CI -1.18, 0.14)	Non significant reduction in systolic and diastolic blood pressure.

Table 36 - Prospective studies

Reference/ country	Population description	Follow up	Mean 25(OH)D	Results/ comments
Cardiovascular disease				
Messenger et al 2012 US	Men participating in the Osteoporotic Fractures in Men study (MrOS) n=821 ≥65 years	4.4 years (median)	CVD event – 62.6nmol/L (49 – 74.1) No CVD event – 63.4nmol/L (50.9-75.1) Q1 - 12.2-50.2nmol/L Q2 – 50.4-62.9nmol/L Q3 – 63.1-75.1nmol/L Q4 – 75.3-138.3nmol/L	Q1: HR 1.18 (95%CI 0.69, 2.03) Q2: HR 1.11 (95%CI 0.65, 1.91) Q3: HR 0.97 (95%CI 0.57, 1.64) Q4: HR 1.00 Ref P=0.85 No significant association between 25(OH)D & CVD outcomes in older men.
Welsh et al 2012 West Scotland	Participants in the MIDSPAN Family Study n=1040 men, 1298 women	14.4 years (median)	46.4nmol/L (median) 33.1% <37.5nmol/L	25(OH)D deficiency (<37.5nmol/L) n=689 HR 1.00 (95%CI 0.77, 1.31) After adjustment no association between 25(OH)D & CVD.
Karakas et al 2013 Germany	Participants in the MONICA survey and the Cooperative Health Research in the Region of Augsburg study 1783 healthy middle aged subjects (964 men, 819 women) 289 cases of CHD (225 men, 73 women)	11 years	Men CHD cases – 37.7nmol/L (1.03) Non cases – 43.9nmol/L (1.02) Women CHD cases – 31.9nmol/L (1.05) Non cases – 39.7nmol/L (1.01)	Men T1 – 27nmol/L (5.08-35.02): HR 1.00 Ref T2 – 43.5nmol/L (35.03-54.13): HR 0.66 (95%CI 0.43, 1.02) T3 – 66.9nmol/L (54.14-153.92): HR 0.84 (95%CI 0.52, 1.35) P=0.461 Women T1 – 26.4nmol/L (9.87-33.15): HR 1.00 Ref T2 – 39.6nmol/L (33.16-47.69): HR 0.67 (95%CI 0.35, 1.29) T3 – 58.5nmol/L (47.7-127.69): HR 0.42 (95%CI 0.19, 0.93) P=0.028 Decreased risk of CHD associated with higher 25(OH)D: more pronounced in women than in men.

Robinson et al 2013 US	Participants in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort study Mean age: 62 years Male: 47% 361 CVD events: MI – 139 cases CHD death: 46 cases Resuscitated cardiac arrest: 13 cases Angina: 163 cases	8.5 years (median)	63.6nmol/L (26.5)	All participants <85.92nmol/L OR 1.32 (95%CI 0.95, 1.83) 85.92-124.58nmol/L OR 1.20 (95%CI 0.95, 1.83) ≥124.58nmol/L OR 1.00 Ref Per 42.95 decrement OR 1.15 (95%CI 1.01, 1.32) P=0.04 *White participants* Per 42.95 decrement OR 1.26 (95%CI 1.06, 1.49) p=0.008 *Chinese participants* Per 42.95 decrement OR 1.67 (95%CI 1.07, 2.61) p=0.03 *Black participants* Per 42.95 decrement OR 0.93 (95%CI 0.73, 1.20) p=0.59 *Hispanic participants* Per 42.95 decrement OR 1.01 (95%CI 0.77, 1.33) p=0.95 Lower 25(OH)D associated with significant higher risk of CHD among white & Chinese participants.No association among black & Hispanic participants.
Perna et al 2013 Germany	Participants in the ESTHER cohort study 7709 participants in the cohort Male: 40.7% 50-74 years 854 non fatal CVD event 176 fatal CVD event 460 non fatal CHD event 79 fatal CHD event 313 non fatal stroke 41 fatal stroke	6.5 years	<30nmol/L – 1114 participants 30-<50nmol/L 3430 participants ≥50nmol/L 3165 participants	*Total CVD* <30nmol/L (171 cases): OR 1.24 (95%CI 1.02, 1.50) 30-<50nmol/L (448 cases): OR 1.14 (95%CI 0.99, 1.32) ≥50nmol/L (392 cases): OR 1.00 Ref Per 25nmol/L (1011 cases): OR 0.95 (95%CI 0.89, 1.01) *Total CHD* <30nmol/L (92 cases): OR 1.32 (95%CI 1.02, 1.72) 30-<50nmol/L (236 cases): OR 1.19 (95%CI 0.98, 1.45) ≥50nmol/L (208 cases): OR 1.00 Ref Per 25nmol/L : OR 0.92 (95%CI 0.84, 1.01) *Total stroke* <30nmol/L (64 cases): OR 1.31 (95%CI 0.95, 1.81) 30-<50nmol/L (165 cases): OR 1.2 (95%CI 0.94, 1.54) ≥50nmol/L (124 cases): OR 1.00 Ref Per 25nmol/L: OR 0.91 (95%CI 0.81, 1.02) Increased risk with levels below 75nmol/L.

Kuhn et al 2013 Germany	2132 participants in EPIC-Germany MI – 559 Stroke – 471 42.1% male Mean age – 50.6 years	7.6 years	All – 47.2nmol/L (±18.3) MI cases – 44.6nmol/L (±18.9) Stroke cases – 44.6nmol/L (±18.3) Non cases – 47.3nmol/L (±18.3)	*MI* Q1 – 28.9nmol/L: HR 1.17 (95%CI 0.86, 1.58) Q2 – 40.4nmol/L: HR 1.07 (95%CI 0.78, 1.45) Q3 – 50.5nmol/L: HR 0.85 (95%CI 0.62, 1.17) Q4 – 66.5nmol/L: HR 1.0 Ref P=0.19 *Stroke* Q1 HR 1.25 (95%CI 0.92, 1.70) Q2 HR 0.83 (95%CI 0.61, 1.14) Q3 HR 0.83 (0.60, 1.13) Q4 HR 1.0 Ref P=0.19 *CVD as composite endpoint* Q1 HR 1.19 (95%CI 0.93, 1.52) Q2 HR 0.96 (95%CI 0.75, 1.24) Q3 HR 0.84 (95%CI 0.65, 1.09) Q4 HR 1.0 Ref P=0.12 No significant association with MI, stroke/VD as composite endpoint *MI* <25nmol/L HR 1.56 (95%CI 1.08, 2.25) p=0.02 25-49.9nmol/L HR 1.10 (95%CI 0.87, 1.39) p=0.43 ≥50nmol/L HR 1.0 Ref *Stroke* <25nmol/L HR 1.54 (95%CI 1.05, 2.27) p=0.03 25-49.9nmol/L HR 0.95 (95%CI 0.75, 1.19) p=0.65 ≥50nmol/L HR 1.0 Ref *CVD as composite endpoint* <25nmol/L HR 1.53 (95%CI 1.12, 2.09) p<0.01 25-49.9nmol/L HR 1.01 (95%CI 0.84, 1.22) p=0.90 ≥50nmol/L HR 1.0 Ref 25(OH)D <25nmol/L significantly increased risk of MI, stroke & CVD. SNP score not related to total CVD risk (HR 1.0 (95%CI 0.71, 1.42).

All-cause mortality

Table 37. Systematic reviews

Study	Methods	Results	Conclusions
Bjelakovic et al 2014 Vitamin D supplementation for prevention of mortality in adults (Review)	Selection criteria: *Inclusion*: Randomised controlled trials that compare any type of vitamin D in any dose, any duration & route of administration versus a placebo or no intervention. Adult participants from the general population or from patients diagnosed with a disease in a stable phase. Supplement vitamin D or active from of vitamin D. *Exclusion:* Patients with secondary induced osteoporosis, pregnant and lactating women, patients with cancer. Outcome measure All-cause mortality	56 trials, 95,286 participants, mean age 18-107 years, 77% women All trials RR 0.97 (95%CI 0.94, 0.99) p=0.02 Vitamin D_3 trials – 13 trials, 12609 participants RR 0.92 (95%CI 0.85, 1.00) p=0.06 Vitamin D_2 trials – 8 trials, 17079 participants RR 1.02 (95%CI 0.96, 1.12) p=0.40	Overall vitamin D supplementation decreased mortality. In an analysis of the different types of vitamin D supplementation (D2 and D3) given without calcium there was no significant effect on mortality.
Schottker et al 2014 Vitamin D and mortality: meta-analysis of individual participant data from a large consortium of cohort studies from Europe and the United States	Selection criteria: *Inclusion*: Cohort studies with study participants aged 50-79 years *Exclusion*: Smokers, study participants with missing 25(OH)D measurements, missing values for covariates used in the main model, or participants lost to follow up due to unknown reasons. Outcome measure All-cause mortality	8 cohort studies form USA and Europe, 26018 participants, 50-79 years, median 25(OH)D concentrations ranged 24-62nmol/L. Highest vs lowest quintile of 25(OH)D RR 1.57 (95%CI 1.36, 1.81)	There was an increased risk of all-cause mortality in the lowest quintile compared to the top quintile of 25(OH)D concentration

Study	Methods	Results	Conclusions
Chowdhury et al 2014 Vitamin D and risk of cause specific death: systematic review and meta-analysis of observational cohort and randomised intervention studies	Selection criteria: *Inclusion:* studies that assessed association of 25(OH)D concentration with specific all cause deaths in adults. Participants recruited from the general population or people with pre-existing baseline conditions. Cohort studies. Intervention studies were eligible if they were randomised; assessed effects of vitamin D supplements singly compared with a placebo or no treatment; and collected cause specific or all-cause mortality endpoints. *Exclusion:* no relevant exposure of outcome data, reviews, letter or editorials, case reports, in vitro/functional studies, non-adult population, inappropriate baseline population, non-randomised trials. Outcome measure All-cause mortality	27 primary prevention cohorts, 780990 participants RR 1.35 (95%CI 1.22, 1.49)	Vitamin D3 supplementation significantly reduced overall mortality in older adults.

Table 38. Prospective studies

Reference/ country	Population description	Follow up	Mean 25(OH)D	Results/ comments
Formiga et al 2014 Spain	Community dwelling older adults n=328 >85 years 39.4% male	2.8 years (median)	70nmol/L (±75) Q1: <34.94nmol/L Q2: 34.94-61.65nmol/L Q3: 61.66-83.37nmol/L Q4: >83.37nmol/L	Q1 OR 1.28 (95%CI 0.61, 2.6) p=0.41 Q2 OR 1.36 (95%CI 0.67, 2.74) Q3 OR 0.76 (95%CI 0.34, 1.68) Q4 OR 1.00 Ref There was no association between baseline serum 25(OH)D and overall mortality in older community dwelling adults.

Skaaby et al 2013 Denmark	General population from 2 population based studies (Monica10 and Inter99) n=9146 Mean age: Monica10 – 55.4years Inter99 – 49.2	10.2 years	Monica10 61nmol/L (44.7-80.9) Inter99 48nmol/L (32-65) (median)	Per 10nmol/L increase OR 0.95 (95%CI 0.92, 0.99) p=0.005 Q1 OR 1.00 Ref p=0.041 Q2 OR 0.79 (95%CI 0.64, 0.98) Q3 OR 0.81 (95%CI 0.65, 1.01) Q4 OR 0.73 (95%CI 0.57, 0.92) 25(OH)D concentration was significantly associated with all-cause mortality.
De Boer et al 2012 US	Participants in the Cardiovascular Health Study n=1621 Caucasian >65 years	11 years (median)	Winter (Jan-March) – 56nmol/L (±24) Spring (April-June) – 63nmol/L (±24) Summer (July-Sept) – 74nmol/L (±25) Autumn (Oct-Dec) – 69nmol/L (±26)	Normal levels HR 1.00 Ref Low level (season specific ranges 43-61nmol/L) HR 1.32 (95%CI 1.14, 1.53) There was an association between lower 25(OH)D concentrations and increased risk of mortality in the Cardiovascular Health Study.
Wong et al 2013 Australia	Participants from the Health in Men Study (HIMS) n=4203, 1144 deaths Mean age 76 years (70-88)	6.7 years		Per 10nmol/L decrease OR 1.04 (95%CI 1.01, 1.07) Halving of 25(OH)D OR 1.21 (95%CI 1.08, 1.35) Q1 10-52.8nmol/L OR 1.20 (95%CI 1.02, 1.42) Q2 52.9-67.3nmol/L OR 1.0 Ref Q3 67.4-81.6nmol/L OR 0.99 (95%CI 0.84, 1.17) Q4 81.7-238.4nmol/L OR 0.99 (95%CI 0.83, 1.17) Low vitamin D status predicted all-cause mortality.

Sempos et al 2013 US	Participants in the NHANES III study n=11315, 3784 deaths Age: 45 years 49% male	15 years	<20nmol/L – n=251, 79 deaths 20-29nmol/L – n=1270, 297 deaths 30-39nmol/L – n=2340, 592 deaths 40-49nmol/L – n=2790, 694 deaths 50-59nmol/L – n=2526, 668 deaths 60-74nmol/L – n=3046, 775 deaths 75-99nmol/L – n=2156, 533 deaths 100-119nmol/L – n=518, 110 deaths ≥120nmol/L – n=202, 36 deaths	<20nmol/L RR 1.6 (95%CI 1.2, 2.2) 20-29nmol/L RR 1.5 (95%CI 1.2, 1.8) 30-39nmol/L RR 1.3 (95%CI 1.1, 1.5) 40-49nmol/L RR 1.1 (95%CI 0.96, 1.3) 50-59nmol/L RR 1.2 (95%CI 1.01, 1.3) 60-74nmol/L RR 1.1 (95%CI 0.99, 1.3) 75-99nmol/L RR 1.0 Ref 100-119nmol/L RR 1.1 (95%CI 0.9, 1.4) ≥120nmol/L RR 1.4 (95%CI 0.9, 2.2) There is a J shaped association.

Autoimmune disease meta-analyses

Table 39. Systematic reviews

Study	Methods	Results	Conclusions
Antico et al 2012 Can supplementation with vitamin D reduce the risk or modify the course of autoimmune disease? A systematic review of the literature	Selection criteria: *Inclusion*: geo-epidemiological studies on the levels of vitamin D and autoimmune diseases in different geographical areas, and physiopathological-clinical studies of the incidence and prevalence of autoimmune diseases in relation to the levels of vitamin D. Type of study included: cross-sectional studies that set in relation to the levels of vitamin D and/or their effects on the clinical course of already diagnosed autoimmune disease (AID); prospective studies correlating the levels of vitamin D with the risk of developing AID; studies relating to the administration of vitamin D and the risk of developing AID; studies evaluating the effect of the administration of the hormone on patients known to have AIDs. Studies of basic science, genetics and experimental studies on animal models which highlighted the role of vitamin D in the pathogenesis of AID were also taken into consideration. *Exclusion:* Not reported. Outcome measure Whether low levels of vitamin D can be correlated with the risk of developing AIDs and whether the administration of the hormone can modify the incidence of the disease or modify the course of autoimmune pathologies.	Vitamin D supplementation in infancy and risk of developing autoimmune disease – type 1 diabetes 9 case-control studies OR 0.71 (95%CI 0.60, 0.84)	The risk of type 2 diabetes was significantly reduced in infants supplemented with vitamin D compared to those not supplemented.

Study	Methods	Results	Conclusions
Harvey et al 2014 Vitamin D supplementation in pregnancy: A systematic review	Selection criteria: *Inclusion:* observational studies (case-control, cohort, cross-sectional), intervention studies. *Exclusion:* studies not in English, were non human studies, did not measure maternal vitamin D status in or immediately after pregnancy or supplement participants with Vitamin D in pregnancy, or where an outcome of interest was not measured. Systematic reviews. <u>Outcome measure</u> Offspring: birthweight, birth length, head circumference, bone mass, anthropometry & body composition, risk of asthma & atopy, small for gestational dates, preterm birth, type 1 diabetes, low birth weight, serum calcium concentration, blood pressure and rickets. Mother: preeclampsia, gestational diabetes, risk of caesarean section and bacterial vaginosis.	Asthma & atopy 10 observational studies Atopic disorders 2 observational studies	Only observational studies on asthma were available. No conclusion could be drawn on asthma as there was substantial heterogeneity in terms of study design, outcome definition and exposure definition and gave a variety of results. Atopic disorders One study showed maternal 25(OH)D concentration was not associated with atopic sensitisation to potential allergens at 5 years, whereas other study showed a positive association with cord blood ≥100nmol/l.

Study	Methods	Results	Conclusions
Multiple sclerosis			
Huang & Xie (2012) Polymorphisms in the vitamin D receptor gene and multiple sclerosis risk: a meta-analysis of case-control studies	Selection criteria: *Inclusion*: Evaluation of the VDR polymorphisms and the risk of MS; case-control design based on unrelated individuals; and sufficient data for genotype distributions on both cases and controls. *Exclusion*: No control; no usable data reported Outcome measure To investigate the association between VDR gene polymorphisms and the risk of MS.	11 case-control studies; 2599 cases with MS & 2816 controls. 2 studies conducted in Asians, 9 studies conducted in Caucasians ***Apa-I polymorphism (rs7975232)*** 4 studies; 599 cases & 878 controls (3 studies in Caucasians , 1 study in Asians) Dominant model: OR 0.71 (95%CI 0.46, 1.12) p=0.14 Recessive model: OR 1.09 (95%CI 0.85, 1.38) p=0.51 Homozygote model: OR 0.72 (95%CI 0.39, 1.36) p=0.32 *Subgroup analysis by ethnicity (Caucasian subjects only)* Dominant model: OR 0.90 (95%CI 0.69, 1.17) p=0.43 Recessive model: OR 1.14 (95%CI 0.88, 1.49) p=0.33 Homozygote model: OR 0.93 (95%CI 0.53, 1.63) p=0.79 ***Bsm-I polymorphism (rs1544410)*** 3 studies; 352 cases & 582 controls (2 studies in Caucasians, 1 study in Asians) Dominant model: OR 0.81 (95%CI 0.36, 1.80) p=0.60 Recessive model: OR 1.17 (95%CI 0.83, 1.64) p=0.38 Homozygote model: OR 1.48 (95%CI 0.90, 2.45) p=0.12 *Subgroup analysis by ethnicity (Caucasian subjects only & dominant model only)* Dominant model: OR 1.09 (95%CI 0.48, 2.46) p=0.84 ***Fok-I polymorphism (rs10735810)*** 6 studies; 1775 cases &1830 controls (6 studies in Caucasians) Dominant model: OR 0.99 (95%CI 0.87, 1.14) p=0.93 Recessive model: OR 0.89 (95%CI 0.74, 1.07) p=0.21 Homozygote model: OR 0.90 (95%CI 0.74, 1.11) p=0.33 ***Taq-I polymorphism (rs731236)*** 8 studies; 2472 cases & 2446 controls (8 studies in Caucasians) Dominant model: OR 1.12 (95%CI 1.00, 1.26) p=0.06 Recessive model: OR 1.03 (95%CI 0.88, 1.20) p=0.74 Homozygote model: OR 1.04 (95%CI 0.78, 1.38) p=0.80	The VDR Apa-I, BSM-I, Fok-I and Taq-I polymorphisms were not associated with MS risk.

Study	Methods	Results	Conclusions
Tizaoui et al 2014 Association between vitamin D receptor polymorphisms and multiple sclerosis: systematic review and meta-analysis of case-control studies	Selection criteria: *Inclusion:* Case control studies that reported the number of individual genotypes and/or alleles for VDR polymorphisms in cases and controls. Each study had disease outcome definitions that followed accepted diagnostic guidelines. *Exclusion:* Cross-sectional studies, size of cases and controls not reported. Outcome measure The association of VDR polymorphisms with MS risk.	13 case-control studies TaqI polymorphism (rs731236) 10 studies: 2104 cases & 2234 controls OR 0.90 (95%CI 0.78, 1.04) p=0.163 BsmI polymorphisms (rs1544410) 3 studies: 494 cases & 552 controls OR 0.91 (95%CI0.51, 1.64) p=0.771 ApaI polymorphism (rs7975232) 5 studies: 630 cases & 921 controls OR 1.30 (95%CI 1.05, 1.60) p=0.013 FokI polymorphism (rs2228570) 6 studies: 1256 cases & 1258 controls OR 1.24 (95%CI 0.99, 1.56) p=0.059	There was no significant association between TaqI and BsmI polymorphisms and multiple sclerosis risk There was a significant association between the ApaI polymorphism and multiple sclerosis pathogenesis but this was only observed in two of the genetic models (homozygous and codominant); the FokI polymorphism was significantly associated with multiple scleosis but only after exclusion of one of the studies following sensitivity analysis. It was also noted that the FokI polymorphism influences Vdr protein structure but that ApaI does not.

Table 40. Trials of vitamin D and autoimmune disease

Study/year/ country	Study population	Intervention	Baseline 25(OH)D	Post intervention 25(OH)D	Outcome	Results	Comments
Asthma							
Goldring et al 2013 London, UK	Pregnant women at 27 weeks gestation n=180 women (88% offspring at age 3 years)	1. 20µg ergocalciferol/d 2. 5000µg cholecalciferol (once) 3. No vitamin D	%.of participants <25nmol/L 1. 48% 2. 45% 3. 42%	Child 25(OH)D concentration at age 3 years (median) 1.32nmol/l (21-66) 2. 42nmol/l (30-93) 3. 42nmol/l (27-68)	Risk of wheeze in offspring at 3 years	HR 0.86 (95%CI 0.49, 1.50) p=0.69	There was no significant difference in risk of wheeze between treatment groups. There was also no difference between groups in prevalence of eczema or atopy.
Rheumatoid arthritis							
Racovan et al 2011 US	Participants in the Women's Health Initiative Study of calcium and vitamin D. n=36,282 50-79 years	1. 10µg vitamin D3 & 100mg calcium 2. Placebo 5.1 years follow up	Not reported	Not reported	Rheumatoid arthritis (self reported)	1. 83 cases 2. 80 cases HR 1.04 (95%CI 0.76, 1.41)	There was no significant difference in cases of rheumatoid arthritis between the two groups.

Table 41. Observational studies

Reference/Country	Population Description	Follow-up	25(OH)D measurement baseline	OR (95%CI)	Results
Tolppanen et al 2013 UK	Children aged 9.8 years in the AVON Longitudinal Study of Parents and Children (ALSPAC) Wheezing n=3323, 141 cases Asthma n=3323, 464 cases Flexural dermatitis n=3748, 300 cases	Not reported	Not reported	$25(OH)D_2$ Wheezing OR 0.83 (95%CI 0.68, 1.00) Asthma OR 0.89 (95%CI 0.78, 1.02) Flexural dermatitis OR 0.83 (9%%CI 0.72, 0.94) $25(OH)D_3$ Wheezing OR 1.14 995%CI 1.03, 1.28) Asthma OR 1.02 (95%CI 0.93, 1.12) Flexural dermatitis OR 1.09 (95%CI 1.00, 1.18)	$25(OH)D_2$ concentration was inversely associated with flexural dermatitis and wheezing. $25(OH)D_3$ was positively associated with flexural dermatitis and wheezing.
Jones et al 2012 Australia	High risk infants in an Australian birth cohort. n=231	12 months	Mean cord blood 25(OH)D3 concentration 58.4nmol/l (24.1)	Per 10nmol/L increase in 25(OH)D OR 0.87 9995%CI 0.77, 0.98) p=0.02	Cord blood 25(OH)D concentration was significantly lower in infants that developed eczema at 12 months. The risk of eczema significantly reduced with increasing cord blood concentration by 10nmol/l.
Mai et al 2012 Norway	Participants in the HUNT population health survey in Norway. Male cases – 208 (mean age 40.3y) Male controls – 885 (mean age 40y) Female cases – 376 (mean age 39.1y) Female controls – 1073 (mean age 39.7y)	11 years	<50nmol/l 47% males cases, 41% controls 45% female cases, 37% controls 50-74.9nmol/l 37% male cases, 35% controls 33% female cases, 40% controls ≥75nmol/l 16% male cases, 24% controls 22% female cases, 23% controls	Men *<50nmol/l* AOR 1.14 995%CI 0.94, 1.37) *50-74.9nmol/l* AOR 1.50 (95%CI 0.95, 2.38) *≥75nmol/l* AOR 1.00 Ref *Per 25nmol/l reduction* AOR 1.14 (0.94, 1.37) Women *<50nmol/l* AOR 0.94 (95%CI 0.67, 1.32) *50-74.9nmol/l* AOR 0.80 (95%CI 0.57, 1.13) *≥75nmol/l* AOR 1.00 Ref *Per 25nmol/l reduction* AOR 0.97 (95%CI0.85, 1.12)	There was no significant association between baseline 25(OH)D concentration and asthma.

Hollams et al 2011 Australia	Participants in a community birth cohort. n=989 6yr olds n=1380 14yr olds		At age 14 years 4.4% <50nmol/l 59.3% >75nmol/l 36.3% 50-75nmol/l	Asthma OR 0.11 (95%CI 0.02, 0.84) p=0.033 Atopy OR 0.14 (95%CI 0.04, 0.47) p=0.002	25(OH)D concentration was inversely associated with developing atopy and asthma at 14 years.
Chawes et al 2014 Denmark	Participants in the Copenhagen Prospective studies on Asthma in Childhood at risk mother-child cohort. n=257 children	7 years	47.6nmol/l (10-145nmol/l) (median)	Troublesome lung symptoms (TROLS) <50nmol/l vs >75nmol/l HR 2.65 (95%CI 1.02, 6.86) p=0.04 Asthma <50nmol/l vs >75nmol/l HR 1.60 (95%CI 0.49, 5.22) p=0.31	Cord 25(OH)D concentration was associated with a significant increase in risk of recurrent TROLS. Cord blood 25(OH)D concentration had no association with asthma at 7 years.

Rothers et al 2011	Participants in the Tuscon Infant Immune Study. n=219	Allergic rhinitis at 3 and 5 years. Asthma 1,2,3 and 5 years	Cord blood 64nmol/l (49-81nmol/l interquartile range) (median)	Log total IgE (n=207) *<50nmol/l* Coef 0.27 (95%CI 0.08, 0.47) p=0.007 *50-74.9nmol/l* Coef 1.00 ref *75-99.9nmol/l* Coef 0.00(95%CI -0.21, 0.20) p=0.99 *100nmol/l +* Coef 0.27 (95%CI -0.00, 0.54) p=0.054 Detectable inhalant IgE (n=208) *<50nmol/l* Coef 2.8 (95%CI 1.2, 6.6) p=0.02 *50-74.9nmol/l* Coef 1.00 ref *75-99.9nmol/l* Coef 2.1 (95%CI 0.9, 4.7) p=0.08 *100nmol/l +* Coef 3.6 (95%CI 1.2, 10.5) p=0.02 Allergic Rhinitis (n=192) *<50nmol/l* OR 1.1 995%CI 0.4, 2.9) p=0.81 *50-74.9nmol/l* OR 1.00 Ref *75-99.9nmol/l* OR 0.6 (95%CI 0.2, 1.8) p=0.38 *100nmol/l+* OR 2.4 (95%CI 0.8, 7.3) p=0.11 Asthma (n=194) *<50nmol/l* OR 0.5 (95%CI 0.2, 1.6) p=0.26 *50-74.9nmol/l* OR 1.00 Ref *75-99.9nmol/l* OR 1.1 (95%CI 0.4, 3.1) p=0.84 *100nmol/l +* OR 1.4 (95%CI 0.4, 5.4) p=0.58	Compared to a 25(OH)D concentration 50-74.9nmol/l, 25(OH)D concentrations <50nmol/l and ≥100nmol/l were significantly associated with increased total IgE concentrations and detectable inhalant allergen-specific IgE. There was no significant association between 25(OH)D concentrations and allergic rhinitis or asthma.

Weisse et al 2013	Participants in the Lifestyle and environment factors and their influence on newborn allergy risk (LINA cohort) n= 378 mother child pairs	2 years	Cord blood – 27.3nmol/l (median) Maternal at 34 weeks – 55.4nmol/l	Association with maternal 25(OH)D concentration (Q4 – 80-152nmol/l vs Q1 – 15-36nmol/l) *1st year of life* OR 1.27 (95%CI 0.67, 2.40) p=0.469 *2nd year of life* OR 3.66 (95%CI 1.36, 9.87) p=0.010 *2 year lifetime* OR 1.91 (95%CI 1.09, 3.37) p=0.025 Association with cord blood 25(OH)D concentration (Q4 43.4nmol/l vs Q1 3.7-17.4nmol/l) *1st year of life* OR 0.92 (95%CI 0.45, 1.85) p=0.812 *2nd year of life* OR 4.65 (95%CI 1.50, 14.48) p=0.008 *2 year lifetime* OR 1.70 (95%CI 0.92, 3.14) p=0.089	Maternal and cord blood 25(OH)D concentration was positively associated with children's risk for food allergy within the first 2 years after birth.
Type 1 diabetes					
Simpson et al 2011 US	Participants in the Diabetes Autoimmunity Study in the Young study. Children at increased risk of type 1 diabetes, age 9m-10y. n=2644	8 years	Only reported in a graph.	Risk of islet autoimmunity HR 1.12 (95%CI 0.88, 1.43) p=0.36 Risk of progression into diabetes HR 0.91 (95%CI 0.68, 1.22) p=0.54 Risk of IA in children age 9m HR 1.02 (95%CI 0.96, 1.07) p=0.58	25(OH)D concentration was not associated with the risk of islet autoimmunity or progression to diabetes in islet autoimmunity positive children.. There was no association between 25(OH)D concentration and risk of islet autoimmunity in 128 infants aged 9 months.
Munger et al 2012 US	Active duty military personnel with serum in the US Department of Defense Serum Repository. 310 cases 613 controls	5.4 years	Cases – 93.2nmol/L Controls – 97nmol/L	<75nmol/L 1.0 Ref 75-<100nmol/L RR 0.60 (0.38, 0.97) ≥100nmol/L RR 0.56 (95%CI 0.35, 0.90) P=0.03	In non Hispanic white subjects with a 25(OH)D concentration >100nmol/L there was a 44% lower risk of developing type I diabetes compared to subjects with a 25(OH)D concentration <75nmol/L.

Sorensen et al 2012 Norway	Women who gave birth in Norway between 1992 and 1994. Cases – 109 (gave birth to a child that subsequently developed type I diabetes before the age of 15 years) Controls - 219	9 years	Cases – 65.8nmol/L Controls – 73.1nmol/L	≤54nmol/L OR 2.38 (95%CI 1.12, 5.07) >54nmol/L OR 1.78 (95%CI 0.85, 3.74) >69 ≤89nmol/L OR 1.35 (95%CI 0.63, 2.89) >89nmol/L OR 1.0 Ref	There was an association between lower levels of maternal 25(OH)D concentrations and an increased risk in type I diabetes in their child before the age of 15 years.
Multiple sclerosis					
Salzer et al 2012 Sweden	Cases with multiple sclerosis that had prospectively drawn blood samples. Cases – 192 Controls – 384 Gestational cases – 37 Gestational controls - 185	9 years	Cases – 40nmol/L (0-122nmol/L) Controls – 39nmol/L (0-158nmol/L) Gestational cases – 39nmol/L (19-103nmol/L) Gestational controls – 40nmol/L (0-335nmol/L)	≥75nmol/L vs <75nmol/L OR 0.39 (95%CI 0.16, 0.98) Gestational 25(OH)D ≥75nmol/L vs <75nmol/L OR 1.8 (95%CI 0.53, 5.8)	Serum 25(OH)D concentration ≥ 75 nmol/L was associated with a decreased risk of multiple sclerosis. No association was found between gestational serum 25(OH)D concentration and multiple sclerosis risk in offspring.

Infectious disease

Table 42. Meta-analysis

Study	Methods	Results	Conclusions
Tuberculosis			
Nnoaham and Clarke 2008 Low serum vitamin D levels and tuberculosis: a systematic review and meta-analysis	Selection criteria: *Inclusion:* Community or hospital based studies, examining the association of vitamin D deficiency and tuberculosis, studied untreated adult tuberculosis patients, used a control group compared to the cases, dealt with mycobacterium tuberculosis *Exclusion:* Studies dealing with other mycobacteria. Outcome measure Tuberculosis	7 studies, 531 participants Random effect size 0.68 (95%CI 0.43, 0.93)	Low serum vitamin D levels are associated with higher risk of tuberculosis.

Gao et al 2010 Vitamin D receptor genetic polymorphisms and tuberculosis: updated systematic review and meta-analysis	Selection criteria: *Inclusion:* Case-control and cohort studies with original data on the association between VDR polymorphisms and TB. Only polymorphisms FokI: rs10735810 C>T, TaqI: rs731236 T>C, ApaI: rs7975232 A>C, BsmI: rs1544410 A>G were considered. *Exclusion:* studies not in English or Chinese, studies on FokI, TaqI, ApaI and BsmI polymorphisms, articles addressing meta-analysis of the association between VDR polymorphisms and TB. Outcome measure Tuberculosis	23 studies: 13 studies in Asian populations, 8 studies in Africans, 2 studies in South Americans *Genotype FokI* Asian population (12 studies): OR 2.0 (95%CI 1.3, 3.2) p<0.1 African population (5 studies): OR 1.0 (95%CI 0.7, 1.3) p=0.8 South American population: OR 0.8 (95%CI 0.4, 2.0) p=0.6 All studies (2 studies): OR 1.5 (95%CI 1.1, 2.0) p<0.1 *Genotype TaqI* Asian population (10 studies): OR 1.4 (95%CI 0.9, 2.1) p=0.1 African population (8 studies): OR 1.1 (95%CI 0.6, 2.1) p=0.7 South American population (2 studies): OR 1.8 (95%CI 0.5, 6.4) p=0.4 All studies: OR 1.3 (95%CI 0.9, 1.9) p=0.2 *Genotype ApaI* Asian population (6 studies): OR 1.3 (95%CI 0.4, 4.5) p=0.7 African population (6 studies): OR 1.8 (95%CI 1.2, 2.8) p<0.1 All studies: OR 0.9 (95%CI 0.7, 1.2) p=0.4 *Genotype BsmI* Asian population (6 studies): OR 0.5 (95%CI 0.4, 0.8) p<0.1 African population (4 studies): OR 1.2 (95%CI 0.8, 1.6) p=0.4 All studies: OR 0.8 (95%CI 0.6, 1.3) p=0.2	Among Asian populations, there was a positive association with FokI ff genotype, a significant inverse association for the BsmI bb genotype and marginal significant associations for TaqI and ApaI polymorphisms. There was no significant association between any of the polymorphisms and TB among African or South American populations.

Lewis et al 2005 Meta-analysis of vitamin D receptor polymorphisms and pulmonary tuberculosis risk	Selection criteria: *Inclusion:* Studies reporting *FokI* (rs10735810) and *TaqI* (rs731236) genotype frequencies in pulmonary TB (PTB) patients and control were included *Exclusion:* Outcome measure Pulmonary tuberculosis	8 case-control studies *FokI* 6 studies (841 cases, 1419 controls) Ff vs FF OR 1.12 995%CI 0.67, 1.86) fF vs FF OR 0.99 (95%CI 0.81, 1.22) *TaqI* 8 studies (1614 cases, 1883 controls) tt vs TT OR 1.00 (95%CI 0.59, 1.70) Tt vs TT OR 0.95 (95%CI 0.80, 1.14)	The results were inconclusive, as the studies were underpowered .
Respiratory tract infections			
Mao and Huang 2014 Vitamin D supplementation and risk of respiratory tract infections: a meta-analysis of randomized controlled trial	Selection criteria: *Inclusion*: RCT study design; healthy patients; exposure was vitamin D supplementation; outcome of interest was RTI; relative risk was reported for vitamin D supplementation compared with placebo. *Exclusion*: low quality publications in terms of the modified Jadad score. Outcome measure Respiratory tract infections.	7 RCTs; n= 4827; age range 1-63y (1 RCT conducted in children), vitamin supplementation varied from 7.5µg to 170µg/day, duration 1.75 to 18 months. Vitamin D supplementation and risk of RTI 0.98 (95%CI 0.93, 1.03) (p=0.45)	Vitamin D supplementation did not reduce the risk of respiratory tract infection.
Charan et al 2012 Vitamin D for prevention of respiratory tract infections: a systematic review and meta-analysis	Selection criteria: *Inclusion*: Randomised placebo controlled clinical trials exploring the effect of vitamin D supplementation on respiratory tract infections e.g. influenza, pneumonia, common cold etc. Only clinical trials where results were given in categorical variables. *Exclusion:* Non randomised, clinical trials without controls and clinical trials showing results in continuous variables. Outcome measure Event of respiratory tract infection.	Children and adults; 5 trials; supplementation varied from 10-50µg/d Respiratory tract infection OR 0.58 (95%CI 0.417, 0.812) p=0.001 (random model) OR 0.62 (95%CI 0.488, 0.776) p=0.000 (fixed model) Adult age group: *3 trials* Respiratory tract infection OR 0.54 (95%CI 0.278, 1.063) p=0.075 (random model) OR 0.65 (95%CI 0.472, 0.904) p=0.010 (fixed model) Pediatric age group: *2 trials* Respiratory tract infection OR 0.58 (95%CI 0.416, 0.805) p=0.001 (random model) OR 0.58 (95%CI 0.416, 0.805) p=0.001 (fixed model)	Respiratory tract infections were significantly lower in vitamin D group compared to the control group. When separating out the children and adult studies, the result only remained significant in children.

Bergman et al 2013 Vitamin D and respiratory tract infections: a systematic review and meta-analysis of randomised controlled trials	Selection criteria: *Inclusion:* Randomised trials, reporting incident respiratory tract infection as a primary or secondary outcome. Eligible outcomes included relative measures of infection risk or absolute numbers of patients experiencing at least one episode of RTI. Upper and lower RTI. Studies reporting composite endpoints deemed to mainly reflect infectious episodes were also included. Number of RTI episodes or days with RTI per patient were also considered *Exclusion:* Studies addressing tuberculosis or fungal infections Outcome measure Respiratory tract infection	11 trials, 5660 participants, 50% male, mean age 16 years, mean supplement intake 40µg. OR 0.64 (95%CI 0.49, 0.84) p=0.0014 Daily vitamin D treatment OR 0.51 (95%CI 0.39, 0.67) Large bolus dose of vitamin D (once per month) OR 0.86 (95%CI 0.62, 1.20)	Vitamin D supplementation significantly reduced the risk of RTI. When the studies were separated the protective effect was only significant in the studies that administered daily vitamin D.
Jolliffe et al 2013 Vitamin D in the prevention of acute respiratory infection: systematic review of clinical studies	Selection criteria: *Inclusion:* cross-sectional, case-control, cohort studies or clinical trials in humans investigating the relationship between serum concentration of vitamin D metabolites of clinical manifestations of vitamin D deficiency, or effect of dietary intake or administration of vitamin D or its analogues, on risk of acute respiratory infection or acute exacerbation of asthma or COPD. *Exclusion:* studies relating to TB. Outcome measure Acute respiratory tract infection.	25 studies (4 cross-sectional, 8 case-control and 13 cohort studies) No odds ratio given.	There was an association between low serum 25(OH)D concentration and increased risk of both upper and lower RTI in the observational studies, this was not supported by the results from RCTs, which were conflicting.

Table 43. Randomised controlled trials

Study/year/ country	Study population/ sample size	Intervention/study design/compliance	Baseline 25OHD (nmol/L) & Analytic method	Post intervention 25(OH)D (nmol/L)	Outcome	RR/OR/HR IG vs CG (95% CI)	Exclusion criteria/compliance/other comments
Respiratory tract infection							
Rees et al. (2013)	n= 759 45-75 years Participants were recruited from a larger double blind multi centre vitamin D trial and prevention of large bowel adenomas.	1. 25µg/day D3 (1000IU/day), Calcium (1200mg/day) 2. Placebo Duration: 3y	At enrollment 1.. 61.9nmol/L (24.8ng/ml (8.3)) 2. 63.1nmol/L (25.3ng/ml (8.8)) At start of cold and flu study 1.. 83.1nmol/L (33.3ng/ml (9.9)) 2. 62.6nmol/L (25.1ng/ml (9.1)) IDS liquid phase radioimmunoassay kit.	Not reported	Number of episodes (in winter) URTI 1. 275 (71.1%) 2. 252 (71.8%) Colds 1. 267 (69%) 2. 239 (68.1%) ILI 1. 46 (11.9%) 2. 51 (14.5%)	Episodes of URTI (in winter) RR 0.93 (0.79-1.09) Colds (in winter) RR 0.93 (0.78-1.10) ILI (in winter) RR 0.95 (0.62-1.46)	Vitamin D supplementation with 25µg/d did not significantly reduce the incidence or duration of upper respiratory tract infections in adults with a baseline serum 25 (OH)D level >30nmol/L.
Bergman et al (2012) Sweden	n=140 Patients with antibody deficiency and patients with increased susceptibility to respiratory tract infections but without immunological diagnosis Mean age 1. 55.4 years 2. 50.8 years	1. Vitamin D3 100µg/day 2. placebo Duration: 1 year	1. 51.5nmol/l 2. 46.9nmol/l	Not measured	Primary outcome was an infectious score based on 5 parameters: symptoms from respiratory tract, ears and sinuses, malaise & antibiotic consumption. 1. 202 points 2. 249 points	0.771 (95%CI 0.604, 0.985) p=0.040	Vitamin D was significantly associated with a reduced total infectious score in patients with an increased frequency of respiratory tract infections.

Study/year/ country	Study population/ sample size	Intervention/study design/compliance	Baseline 25OHD (nmol/L) & Analytic method	Post intervention 25(OH)D (nmol/L)	Outcome	RR/OR/HR IG vs CG (95% CI)	Exclusion criteria/compliance/other comments
Urashima et al 2010 Japan	Schoolchildren n=334 6-15 years	1. 30µg/d D3 2. Placebo Duration: 4 months	Not measured	Not measured	Influenza A 1. 18 cases out of 167 children (10.8%) 2. 31 cases out of 167 (18.6%) Influenza B 1. 39 cases out of 167 children (23.3%) 2. 28 cases out of 167 children (16.8%)	Influenza A 0.58 (95%CI 0.34, 0.99) p=0.04 Influenza B 1.39 (95%CI 0.90, 2.15) p=0.13	Influenza A was significantly lower in the supplement group compared to the placebo group. There was no significant difference for Influenza B between the 2 groups.
Chronic obstructive pulmonary disease (COPD)							
Lehouck et al 2012 Belgium	Patients with moderate to very severe COPD n=182 >50 years	1. 2500µg every 4 weeks 2. Placebo Duration: 1 year	1. 50nmol/L (30) 2. 50nmol/L (27)	1. 130nmol/L (40) 2. 55nmol/L (32)	COPD exacerbations per patient per year 1. 2.8 2. 2.9	0.94 (95%CI 0.76, 1.16) p=0.57	There was no difference between the intervention and placebo groups for time for first exacerbation or exacerbation rates.
Pneumonia							
Manaseki-Holland et al 2012 Afghanistan	Infants aged 1-11months n=1524	1. 2.5mg D3 every 3 months 2. Placebo Duration: 18 months	Not reported		Episodes of pneumonia 1. 260 2. 245	All pneumonia RR 1.06 (95%CI 0.89, 1.27) p=0.476	There was no significant difference in the incidence of first or only pneumonia between the vitamin D and placebo group.

Table 44. Observational studies

Reference/Country	Population Description	Follow-up	25(OH)D measurement baseline	OR (95%CI)	Results
Tuberculosis					
Arnedo-Pena et al 2014 Spain	Study population comprised of contacts of pulmonary TB patients (n=89) Cases – 3 Cohort - 520 Mean age Cases – 42.3 (24) Cohort – 38 (14)	1.6 years	Cases - 34.2nmol/L (15.7) Cohort – 64nmol/L (31.7)	HR 0.88(95%CI 0.80, 0.97) p=0.034	An inverse association was found between mean serum 25(OH)D concentration and TB incidence.
Respiratory tract infections					
Belderbos et al 2011 The Netherlands	Healthy term neonates n=156	1 year	Mean: 82nmol/L (3.5) (cord blood) 4%<25nmol/L 23% <50nmol/L 27% 50-74nmol/L 46% ≥75nmol/L	≥75nmol/l vs <50nmol/L RR 6.2 (95%CI 1.6, 24.9) p=0.01	Low 25(OH)D concentrations in the 1st year after birth are associated with increased risk of RSV LRTI.

Camargo et al 2011 New Zealand	Expectant mothers taking part in the New Zealand Asthma and Allergy Cohort Study. n=922 newborns	5 years	44nmol/l (29-78)	*At 3 months of age* *Respiratory infection* <25nmol/L OR 2.04 (95%CI 1.13, 3.67) p=0.03 *Any infection* <25nmol/l OR 2.36 (95%CI 1.17, 4.73) p=0.02 *Wheeze by 15months of age* OR 0.98 (95%CI 0.93, 1.02) p=0.3 *Wheeze by 3y of age* OR 0.96 (95%CI 0.91, 1.00) p=0.04 *Wheeze by 5y of age* OR 0.95 (955CI 0.91, 1.00) p=0.02 *Incident asthma by 5y of age* OR 1.03 (95%CI 0.97, 1.10) p=0.27	Low cord blood 25(OH)D concentration was associated with higher risk of respiratory infection at 3 months of age. Low cord blood 25(OH)D concentration was also associated with wheeze throughout childhood, but not associated with asthma.
Shin et al 2013 Korea	Newborns from a Korean birth cohort n=525	6 months	32nmol/l (21.4-53.2) 180 neonates <25nmol/l 292 neonates 25-74.9nmol/l 53 neonates >75nmol/l	<25nmol/l *Respiratory tract infections* OR 3.41 (95%CI 1.57, 7.42) p=0.0008 *Acute nasopharyngitis* OR 4.64 (95%CI 1.88, 11.44) p=0.0002 *Otitis media* OR 3.06 (95%CI 0.38, 24.46) p=0.3625 *Bronchiolitis* OR 2.74 (95%CI 0.34, 22.11) p=0.4819	Cord blood 25(OH)D concentration was associated with increased risk of acute nasopharyngitis.

Magnus et al 2013 Norway	Participants in the Norwegian Mother and Child cohort study Case-control study at 36 months and current asthma: 489 cases 1183 controls	36 months	73.7nmol/l Collected at 18 weeks gestation 16.8% mothers ≤50nmol/l 34% mothers 51-75nmol/l Case-control study Cases – 68.6nmol/l (23.5) Controls – 73.7nmol/l (23.8)	1-2 LRTIs vs no LRTIs RR 0.98 (95%CI 0.87, 1.12) >3 LRTIs vs no LRTIs RR 0.74 (95%CI 0.58, 0.93) Case-control study (per 20nmol/l increase in 25(OH)D) OR 0.95 (95%CI 0.83, 1.08)	Higher maternal 25(OH)D concentration at 18 weeks gestation was associated with a reduced risk of more than 3 LRTIs versus no LRTIs. There was no association with asthma at 36 months.
Science et al 2013 Canada	Participant in a cluster randomised controlled trial evaluating the effect of influenza vaccination of children on viral infection rates in Hutterite communities. n=743 7-13 years	156 days	62nmol/l (median) (51-74)	<50nmol/l HR 1.67 (95%CI 1.16, 2.40) p=0.006 <75nmol/l HR 1.51 (95%CI 1.10, 2.07) p=0.011	There was an increased risk of viral RTI with 25(OH)D concentrations <50nmol/l and <75nmol/l.
Pneumonia					

Jovanovich et al (2014) US (retrospective matched cohort study)	Community living individuals hospitalized with community acquired pneumonia (CAP) or sepsis. CAP 66 cases 66 controls 60 years (17) 71% female 86% Caucasian Sepsis 211 cases 211 controls 65 years (14) 59% female 91% Caucasian	15 months	CAP Cases – 70.1nmol/L (62.2-79.6) Controls – 79.3nmol/L (71.1-88.1) Sepsis Cases – 61.2nmol/L (55.9-66.4) Controls – 69.1nmol/L (64.2-74.1)	25(OH)D <75nmol/L vs >75nmol/L <u>CAP</u> 1.03 (0.51, 2.09) P=0.93 <u>Sepsis</u> 1.24 (0.84, 1.83) P=0.28 25(OH)D <50nmol/L vs >50nmol/L <u>CAP</u> 0.96 (0.35, 2.61) P=0.96 <u>Sepsis</u> 1.75 (1.11, 2.77) P=0.02 25(OH)D <37nmol/l vs >37nmol/l <u>CAP</u> 2.57 (1.08, 5.08) P=0.03 <u>Sepsis</u> 1.89 (1.09, 3.31) P=0.02	There was an increased risk of hospitalization for CAP with 25(OH)D levels <37nmol/l and for sepsis with 25(OH)D levels <50nmol/l.
Aregbesola et al 2013 Finland	Participants in the population based Kuopio Ischemic Heart Disease Risk Factor study. n=723 men & 698 women 53-73 years	9.8 years	43.5nmol/l (17.8)	Tertile 1 (8.9-33.8nmol/l) RR 2.6 (95%CI 1.4, 5.0) Tertile 2 (33.9, 50.7) RR 1.5 (95%CI 0.7, 2.9) Tertile 3 RR 1.00 Ref P=0.005	Participants in the lowest tertile of 25(OH)D concentration had a higher risk of developing pneumonia.

Table 45. Cross-sectional studies

Reference/ country	Population description	25(OH)D measurement	%	Conclusions
Ginde et al (2009) US	Secondary analysis of the 3rd National Health and Nutrition Examination Survey N=18,883 Median age 38 years 52% female 75% Caucasian	Overall median – 29ng/ml (21-37ng/ml) Reporting a URTI – 28ng/ml Without URTI – 29ng/ml	Serum 25(OH)D <25nmol/L 24 (20-29) Serum 25(OH)D 25 - <75nmol/L 20 (19-22) Serum 25(OH)D >75nmol/L 17 (15-19)	Vitamin D may reduce the risk of URTI.
Berry et al (2011)	n= 6789 Nationwide 1958 British birth cohort Mean age 45 years	<25nmol/l n=523, 7.7% 25-49nmol/l n=2282, 33.6% 50-74nmol/l n=2454, 36.2% 75-99nmol/l n=1112, 16.4% >100nmol/l n=418, 6.2%		Each 10nmol/l increase in 25(OH)D was associated with a 7% lower risk of infection

Neuropsychological functioning

Table 46. Systematic reviews

Study	Methods	Results	Conclusions
Cognition and dementia			
van der Schaft et al 2013 The association between vitamin D and cognition: A systematic review	Selection criteria: *Inclusion*: observational studies where vitamin D was defined as the concentration of vitamin D in serum or as the dietary vitamin D intake, cognition was defined as a score on a cognitive function test, study participants were adults, a measure of association was available. *Exclusion:* animal studies, studies on cognition, but not in association with vitamin D, study about vitamin D but not in association with cognition, study not about vitamin D or cognition, studies in children, study about vitamin D supplementation and no focus on association, expert opinion, no full text available. Outcome measure Cognitive function	25 cross-sectional studies n=48,680, 20-80 years 6 prospective studies n=10,896, 65 years plus, mean follow up 4-7 years (A meta-analysis could not be performed due to the large variability in used measures to assess vitamin D exposure and even larger variability in cognitive function tests and measurement scales used.)	*Cross-sectional studies* A statistically significant worse outcome on one or more cognitive function tests or a higher frequency of dementia with lower vitamin D levels or intake in 72% of studies. Prospective studies A statistically significant decline on one or more cognitive function tests or a higher frequency of dementia in participants with lower vitamin D levels or intake in 67% of the studies.
Depression			
Anglin et al 2013 Vitamin D deficiency and depression in adults: systematic review and meta-analysis	Selection criteria: *Inclusion:* RCTs, case-control studies, cross-sectional studies, cohort studies, adults 18 years plus. Depression reported as outcome of interest and vitamin D measurements as a risk factor or intervention. Cross-sectional and cohort studies were required to report depression outcomes for participants with vitamin D deficiency compared with those with normal vitamin D levels. There was no language restriction. *Exclusion:* Not reported. Outcome measure Depression	1 case-control study, 3 cohort studies, 10 cross-sectional studies (total n=31424) 9 cross-sectional studies Lowest vs highest 25(OH)D OR 1.31 (95%CI 1.0, 1.71) p=0.03 3 cohort studies Lowest vs highest 25(OH)D HR 2.21 (95%CI 1.40, 3.49) p=0.28	There was an increased odds ratio of depression for the lowest vs highest vitamin D in the cross-sectional studies. There was a significant increased hazard ratio of depression for the lowest vs highest categories of 25(OH)D concentration.

Spedding et al 2014 Vitamin D and depression: A systematic review and meta-analysis comparing studies with and without biological flaws	Selection criteria: *Inclusion:* RCTs with vitamin D supplementation *Exclusion:* trials that were not RCTs or used surrogate interventions Outcome measure Depression	15 RCTs were identified, only 2 were included in a meta-analysis, as they were classed as without flaws, as the same depression measure was used. 0.78 (95%CI 0.24, 1.27)	There was a significant improvement in depression.
Schizophrenia			
Valipour et al 2014 Serum vitamin D levels in relation to schizophrenia: a systematic review and meta-analysis of observational studies	Selection criteria: *Inclusion:* observational studies in humans that had measured serum levels of vitamin D in schizophrenic patients. *Exclusion:* No serum vitamin D levels reported Outcome measure Schizophrenia	19 studies (8 cross-sectional, 10 case-control, 1 nested case-control study), n=2804, 18-65 years Mean difference in serum 25(OH)D concentration between schizophrenic patients and control subjects -15nmol/l (95%CI -27, -3nmol/l) Vitamin D deficiency (<50nmol/l) in schizophrenic patients 65% (95%CI 46-85%) 25(OH)D <50nmol/L vs >50nmol/L OR 2.16 (95%CI 1.32, 3.56)	Participants with a 25(OH)D concentration<50nmol/L were more likely to have schizophrenia.

Table 47. Randomised controlled trials

Study/year/ country	Study population/ sample size	Intervention/study design/compliance	Baseline 25OHD (nmol/L) & Analytic method	Post intervention 25(OH)D (nmol/L)	Outcome	RR/OR/HR IG vs CG (95% CI)	Exclusion criteria/compliance/other comments
Cognition and dementia							
Przybelski et al 2008 US	Nursing home residdents with low 25(OH)D levels ≤62.4nmol/L n=63 mean age 87 years	1. 1250µg three times a week 2. No placebo or treatment Duration: 4 weeks Unblinded study	1. 43.2 (3) 2. 86.9 (4.5)	1. 159 (8.5) 2. Remained unchanged	Cognition	Not reported	Vitamin D2 supplementation had no effect on cognition in the intervention group.
Stein et al 2011 Australia	Community dwelling individuals with mild/moderate Alzheimer's disease n=32 started treatment >60 years	All participants: 25µg/d throughout trial After 8 weeks: 1. 300µg 3/times a day & then 0-2/times a day to maintain 130-175nmol/l at 2, 4 and 6 weeks 2. placebo	49nmol/l (39-67) Diasorin, Stillwater, MN	After 8 weeks low dose: 1. 60 (56-70) 2. 64 (48-72) 1.187 (160-240) 2. 72 (63-81)	Cognition	Not reported	High dose of vitamin D had no effect on cognition.
Rossom et al 2012	Participants in the WHI calcium and vitamin D trial & the Women's Health Initiative Memory study n=4143 women >65 years	1. 10µg/d & 1000mg calcium carbonate 2.placebo Duration: 7.8 years	1. 50nmol/L (n=150) 2. 48nmol/L (n=143)	Not reported	Cognition	1. 98 cases of incident mild cognitive impairment 2. 108 cases of incident mild cognitive impairment HR 0.95 (95%CI 0.72, 1.25) p=0.72	There was no effect of vitamin D supplementation on cognition.