NICE Maternal and Child Nutrition Programme

Review 7: The effectiveness and cost-effectiveness of interventions to promote an optimal intake of Vitamin D to improve the nutrition of pre-conceptual, pregnant and post-partum women and children, in low income households.

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A review prepared for NICE by:
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1 Rationale

This rapid systematic review investigates interventions to promote an optimal Vitamin D status to improve the nutrition of pre-conceptual, pregnant and post-partum women and children in low income households. It was commissioned by the National Institute for Health and Clinical Excellence (NICE). It will inform the NICE public health programme guidance for midwives, health visitors, pharmacists and other primary care services to improve the nutrition of pregnant and breastfeeding mothers and children, in low income households.

1.1 Background

Introduction

Vitamin D is essential in the maintenance of skeletal growth and bone health – vitamin D regulates calcium and phosphate absorption and metabolism. As the dietary sources of vitamin D are limited (they include oily fish, fortified margarines, some breakfast cereals and smaller amounts in red meat and egg yolk) the main source is the synthesis following exposure of the skin to sunlight (SACN 2007). About 90% of vitamin D is synthesized in the skin with sunlight exposure and 10% is derived from diet. Serum 25-hydroxyvitamin D (25-OHD) reflects the vitamin D derived from both sources and is considered to be an indicator of the individual's vitamin D status. In the United Kingdom an individual is considered at risk of vitamin D deficiency when serum 25 OHD falls below 25nmol/l (SACN 2007).

There are seasonal variations in vitamin D status in the UK (highest in July to September and lowest January to March) (SACN 2007). During the winter months, there is no ambient ultraviolet light of the appropriate wavelength at UK latitudes (UK lies at a latitude of 50 to 58 degrees north) and the UK population relies on body stores and dietary sources to maintain vitamin D status (SACN 2007). Uptake of vitamin D supplementation in the UK is low and vitamin D deficiency has re-emerged in recent years as a public health concern, particularly for women and children from South Asian and Afro-Caribbean groups (Anonymous. 2006;Ashraf et al. 2002;Callaghan et al. 2002;Crocombe et al. 2004;Datta et al. 2002;Iqbal et al. 1994;Ladhani et al. 2004).

Vitamin D deficiency can occur when the demand for it exceeds supply, as in period of rapid growth in fetal life, infancy, early childhood and puberty, and during pregnancy and lactation. Vitamin D status of the newborn is largely determined by the vitamin D status of the mother. Severe deficiency of vitamin D results in rickets (in children) and osteomalacia (in children and adults). Vitamin D deficiency has also been implicated in a range of other conditions, such as type 1 diabetes, some cancers and cardiovascular disease, but the evidence is less conclusive (SACN 2007). There is also emerging evidence that improved vitamin D status of the mother during pregnancy may have a wider beneficial impact on their child's health including risk of osteoporotic fracture (Javaid 2006) and wheeze (Devereux 2007) in childhood. While concerns have been raised about very high intakes (Gale 2007), in the United Kingdom the guidance level for upper intake of supplementary vitamin D is 25ug/day (SACN 2007). In Europe and the United States the tolerable upper intake level for adults is set at 50 µg/day (EVM 2003). Such intakes are considerably higher than the reference nutrient intake.

Nutritional recommendations

Long standing recommendations on vitamin D intake for the UK population were established by COMA in 1991 (Department of Health, 1991). More recently, the Scientific Advisory Committee on Nutrition (SACN) - the independent committee which superseded COMA - published an update on vitamin D status and other related issues including a synopsis of evidence about the relationship between vitamin D status and chronic disease. SACN reiterated the recommendations of COMA on vitamin D, including the use of supplements to achieve adequate intakes (SACN 2007). In particular, SACN emphasised the advice that all pregnant and breastfeeding women should consider taking a daily supplement of vitamin D (10ug) in order to ensure their own requirement is met and to build adequate fetal stores for early infancy. Although the NICE guidance on antenatal care (2003) concluded that vitamin D supplementation should not be offered routinely to all pregnant women, the Chief Medical Officer (2005) subsequently re-iterated the COMA advice, particularly the importance of offering supplements to women from vulnerable groups. An updated version of the NICE guidance will be available in 2008.

Reference nutrient intakes (RNI)* of 8.5 ug per day and 7ug per day are recommended for infants aged 0-6 months and 6 months to 3 years respectively (COMA 1994, COMA 1998). COMA recommended that children should be given vitamin D supplements up to 3 years of age: breastfed infants to be given supplements from 6 months of age (not required before 6 months provided the mother had adequate vitamin D status in pregnancy); infant formula is fortified with vitamin D and so supplementation to commence when intake falls below 500ml per day. There is no RNI for children aged 4 years and above. [The RNI is the amount of a vitamin or mineral that is enough or more than enough for about 97% of people in a group. If average intake of a group is at the RNI, then the risk of deficiency in the group is very small.]

Sun exposure

In addition to the recommendations above, the Department of Health recommends that an adequate vitamin D status should be achieved from exposure of the skin to summer sunlight, although this needs to be balanced against increasing the risk of skin cancer and public health advice on the use of sunscreen (NHS Direct 2006, Cancer Research UK 2006).

The awareness of the hazards of excessive sunlight exposure in childhood and subsequent development of skin cancer resulted in public health advice from the mid-late 1990s to emphasise shielding the skin from direct sunlight from birth onwards, and the liberal use of sunscreen. (Cancer Research UK. 2006;NHS

Direct. 2006). It has been hypothesised that there may be an association between nutritional rickets and the increasing use of sunscreen in infants and young children who have limited vitamin D intake (Zlotkin 1999). Although the use of sun screen can reduce vitamin D production in the skin a cross sectional UK study among middle aged adults found that sun protection was associated with slightly higher rather than lower 25(OH)D concentrations suggesting that sun protection partly reflects sun exposure and does not strongly interfere with vitamin D synthesis (Hypponen and Power 2007).

During winter at latitudes North of about 52^{o} (the United Kingdom lies at latitudes between 50-60^{o}N) there is no ambient ultraviolet light of the appropriate wavelength to support cutaneous production of previtamin D3. In Spring, Summer and Autumn, 5-15 minutes sun exposure between 10am and 3pm may be adequate for individuals with lighter coloured skin living in the UK (SACN 2007). Consequently there is a policy need to state clearly the length and intensity of exposure necessary to balance maintenance of vitamin D status with the risk of developing skin cancer (SACN 2007).

Current intakes and deficiency

The average dietary intake of young women in the UK is approximately 3 ug per day and fewer than 1% achieve the RNI of 10ug per day. The National Diet & Nutrition Survey (2003) (a predominantly white sample) reported that about 28% of the UK female population aged 19 to 24 years had low serum vitamin D levels (below 25 nmol/l) (Office for National Statistics. 2004) and 13 to 15% of women 25-49 years of age had low serum vitamin D levels. Similarly, the NDNS of 1.5 to 4.5 year olds (2005) found that mean vitamin D intakes from all sources (ie including supplements and fortified foods) was 1.9ug per day, well below the RNI of 7ug per day. In a longitudinal study of a cohort of white women living at one of the most southerly latitudes of the UK (Southampton), 18% of women were reported to be at risk of vitamin D deficiency (25(OH)D <27.5nmol/l) during late pregnancy (34 weeks) and this was associated with reduced bone mineral accrual in the offspring during childhood (Javaid 2006). In 2004-5, there were 84 finished consultation episodes of active rickets compared with 40 in 1998-99 (Department of Health. 2006).

Rickets has been recognized as a problem in children of Asian and black ethnic background in the UK since the 1960s. Infants, toddlers and adolescents in 'at risk' ethnic minorities (Asian, African Caribbean and Middle Eastern) are particularly likely to be vitamin D-deficient or to have rickets (Lawson 1999, Ladhani 2004, Crocombe 2004, Das 2005). In this group, vitamin D deficiency is estimated to occur in around 50% of pregnant women and their neonates (Datta 2002, Brooke 1980), 40% of toddlers (Grundulis 1986, Lawson 1999), 45% of schoolchildren (Ford 1976, Stephens 1982) and over 70% of adolescents (Ellis 1977, Crocombe 2004, Das 2005). A survey in inner city of Birmingham reported that 88% of asymptomatic Asian women were vitamin D deficient compared with 2.3% of non-Asian women (Pal et al. 2001). A 2002 postal survey of 119 consultant paediatricians in the West Midlands identified 24 cases of rickets in children 0-5 years (an incidence of 38, 95 and 0.4 per 100,000 per annum in Asian, black and white children respectively)(Callaghan et al. 2002;Callaghan et al. 2006;Moy et al. 2004). In Burnley, it was reported that although the incidence of deficiency in was 1 in 923 children in the general study population it was 1 in 117 among children of Asian origin (reflecting that 93% of patients were Asian origin) (Zipitis et al 2006). The authors estimated that it cost £2500 to treat hospital-ascertained childhood case of vitamin D deficiency compared to £2400 to provide every child of Asian origin with a 7ug vitamin D supplement for the first two years of life. However the true prevalence of vitamin D deficiency in the local childhood population was not determined in this study.

Supplementation uptake

Maternal consumption of vitamin D supplements improves both maternal and neonatal vitamin D status.

The Infant Feeding Survey (2005) found that 54% of women took some form of vitamin or mineral supplements (apart from folic acid) during pregnancy, although around a third (29%) said that these contained iron only. Whether women took supplements varied by socioeconomic status – 61% of women from managerial and professional occupation groups took supplements compared to 48% of those from routine and manual occupation groups. Among mothers who were breastfeeding, only 33% took a supplement at stage 1 (4 to 10 weeks) and this dropped to 23% by stage 3 (8 to 10 months). Of the breastfeeding women who took a supplement, just under half took a multivitamin / iron combination (41% at stage 1, 46% at stage 2 and 44% at stage 3). However, a significant number took supplements that would not include vitamin D - iron only and/or omega supplements* (37% at stage 1, 18% at stage 2 and 23% at stage 3).
[Omega supplements which contain cod liver oil are contraindicated in pregnancy (and should say so on the label)]

It has been suggested that infant vitamin D supplementation may be more effective than postnatal maternal supplementation (Hollis et al. 2004;Rothberg et al. 1982). However, assessment of clinically diagnosed rickets among children under five in Birmingham PCT in 2006 found that 3 out of 6 of babies presenting with hypocalcaemic convulsions were consuming fortified infant formula, implying that these infants had low stores of vitamin D at birth due to inadequate maternal vitamin D status during pregnancy (Callaghan 2006).

The Infant Feeding Survey (2005)* found that 4% of babies were given vitamin supplements at stage 2 (4 to 6 months of age) and 7% at stage 3 (8 to 10 months of age). There was little change at younger ages since the previous survey in 2000 but a fall from 10% for stage 3 babies. Babies were more likely to be given supplements if they had received special care or were low birthweight (<2.5kg). 25% of Asian and 23% of Black mothers gave their babies supplements at stage 3 compared to only 5% of white mothers. The survey suggests that this difference may be partly due to the fact that Asian and Black babies tend to be smaller on average at birth. Mothers who were breastfeeding were more likely to be giving their baby supplements at stage 3 (16%) than those who were not (6%). [Survey undertaken prior to the introduction of *Healthy Start*]

Other factors associated with deficiency

Factors associated with a higher prevalence of deficiency among at risk groups include increased skin pigmentation, spending limited time outdoors, and cultural and religious practices such as extensive body covering with clothing that restrict exposure to sunlight (Matsuoka 1992). It has also been suggested that low meat intakes (Dunnigan 2005) or a vegetarian diet (Finch 1992) may increase risk of rickets or osteomalacia. However, it remains unclear whether observed associations are due to dietary, religious or cultural practices as studies have focused on particular groups of Asian vegetarians.

Because all infant formulas in the UK are fortified with vitamin D infants of mothers who have low vitamin D status are more likely to develop vitamin deficiency if they are not given supplements and are exclusively breastfed. Infants who are given cows milk as the main drink before one year of age and do not receive supplements are also at increased risk of deficiency.

Policy

An effective population-wide approach to promote dietary vitamin D intake is integral to the improvement of the nutritional status and wellbeing of mothers and children from birth in the UK, as outlined in the Department of Health (DH) initiative *Healthy Start* (DH 2005). Supplements containing 10ug of vitamin D (and vitamin C and folic acid) are available free to all women eligible for Healthy Start and all pregnant women under 18 years of age (during pregnancy and for one year after the birth of their child).

Healthy start children’s vitamin drops containing 7.5ug of vitamin D (and vitamin A and vitamin C) are free to healthy start beneficiaries from 6 months to 4 years of age. All healthy start supplements can be prescribed or purchased at low cost for women and children who are not eligible for the scheme.

Due to the high levels of rickets (Callaghan 2002 and 2006) and in an attempt to increase uptake of supplements, a local health promotion campaign led by the Heart of Birmingham Teaching PCT provides free vitamin supplements for all children under 5 and pregnant and breastfeeding women.
The Food Safety Authority in Ireland published recommendations for a national policy on vitamin D supplementation for infants in Ireland in 2007. The Authority recommended that irrespective of how they are fed, all infants in Ireland should be given a 5ug supplement of vitamin D every day from birth to 12 months of age. A new supplement containing only vitamin D3 (cholecalciferol) is to be made available to implement this recommendation. The Authority has highlighted that "Regardless of whether a baby is breastfed, partially breastfed or fed infant formula during the first year of life, infants are at high risk of having insufficient vitamin D stores….Breast milk with a supplement of vitamin D provides the optimal level of nutrients required by infants in the early stages of life and is known to bestow lifelong health benefits". (FSAI PR, FSAI website).

The fortification of margarine is mandatory in the UK. Reduced fat spreads and many breakfast cereals are fortified on a voluntary basis. Unlike the US and Canada, milk is not fortified in the UK. The Infant Formula and Follow on Formula Regulations state that between 1.0 and 2.5ug/100kcal of vitamin D should be added to all standard infant formulas (ensuring that a 5kg infant ingesting 100 kcal/kg/day will achieve a daily vitamin D intake of at least 5ug).

2 Evidence statements

No	Statement	Grade	Evidence
	Stand alone vitamin supplementation: UK		
1	Evidence from seven studies (five 1+RCTs and two 2+ studies) show that antenatal vitamin D supplementation is effective in improving the vitamin D status of Asian and Caucasian women.	**1+**	Brooke et al. 1980; Maxwell et al. 1981; Cockburn et al. 1980; Datta et al. 2002; Mallet et al. 1986; Delvin et al. 1986; Greer & Marshall, 1989; Greer et al. 1981 & 1982)
2	No adverse effects were reported in any of the studies considering vitamin D supplementation to mothers or infants.		Brooke et al. 1980; Maxwell et al. 1981; Cockburn et al. 1980; Datta et al. 2002; Mallet et al. 1986; Delvin et al. 1986; Greer & Marshall, 1989; Greer et al. 1981 & 1982)
3	Evidence from one 1+ RCT indicates that infants of Asian mothers who received an antenatal vitamin D supplement achieved a higher body weight during the first year after birth than infants of mothers who received no antenatal vitamin D supplement.	**1+**	Brooke et al. 1980; 1981 ; Maxwell 1981
4	A 2+ non RCT found that breast-fed infants of supplemented (10 ug/day) mothers had higher 25 hydroxy vitamin D levels 6 days after birth than breastfed infants of unsupplemented mothers. Vitamin D levels of all breast-fed infants were lower than infants receiving infant formula.	**2+**	Cockburn et al. 1980
5	Evidence from a 1+ RCT suggests that the infants of mothers given supplements during pregnancy (25 ug/day during the third trimester) achieved a higher serum 25 hydroxy vitamin D levels than un-supplemented breastfed infants, at birth and at four days of age.	**1+**	Delvin et al. 1986

6	Evidence from a 1+ RCT indicates that the weights of supplemented (10 ug/day), un-supplemented breast-fed infants and formula-fed infants did not differ at six months.	**1+**	Greer & Marshall, 1989
7	Evidence from two 1+ RCTs indicates that the effect of vitamin D supplements on infant bone mineral content is uncertain. The results from two studies were found to be conflicting.	**1+**	Greer et al. 1981 & 1982; Greer & Marshall, 1989

3 Research questions

3.1 Question 1

What public health interventions are effective in promoting an optimal dietary Vitamin D intake (i.e. which meets the intake recommended by COMA) in the following:

- women planning a pregnancy
- pregnant women
- post-partum women (up to one year following birth) with consideration given to future pregnancies
- infants and young children from birth and up to five years, both breastfed (fully or partially) and formula fed
- particular emphasis was made to lower socio-economic groups, vulnerable groups, including young teenage mothers, refugees and asylum seekers, black and minority ethnic groups and their cultural and religious practices.

3.2 Question 2

What interventions are effective in promoting advice and/or increased uptake of vitamin D supplementation in these population groups? What are the barriers to uptake?

3.3 Question 3

What practices other than supplementation affect vitamin D status in at risk groups and how can they be modified?

4 Inclusion criteria

This review focused on public health interventions to promote an optimal intake of vitamin D and improve the vitamin D status of pre-conceptual, pregnant and post-partum women and children aged 0-5 years, with particular reference to those in low income households. For stand alone vitamin D supplementation, the outcomes of interest were: maternal and infant serum vitamin D levels and body weights changes, infant birth weights, bone mineral content and incidence of rickets and osteomalacia. For interventions to promote dietary vitamin D intake and uptake of vitamin D supplementation, outcomes included uptake of and compliance with the interventions, changes in knowledge, vitamin D status of the participants and changes in numbers of hospital admissions with rickets and osteomalacia. We included all study designs for studies conducted in the UK, but for studies conducted in other developed countries, only systematic reviews and randomized controlled trials were included. Papers in English, published between 1995 and 2006 were considered in the first instance. Due to the paucity of data, the search was then extended to studied published between 1966 and 2006.

4.1 Participants of interest

Participants of interest included pre-conceptual, pregnant and post-partum women, children aged 0-5 years in developed countries from any socio-economic background, with particular emphasis on the following subgroups:

- Mothers and children in lower socio-economic groups
- Mothers and children living in areas of deprivation, including inner city areas
- Mothers and children from black and minority ethnic groups
- Mothers aged under 18 (and their children)
- Unsupported mothers (and their children)
- Mothers and children from groups who are likely to be nutritionally vulnerable, such as refugees and asylum seekers

The review excluded mothers and children with clinical conditions that require specialist advice, secondary dietary management or clinical therapeutic advice, where normal care would be inappropriate. Babies with low birth weight (less than 2500g) were excluded.

4.2 Interventions of interest

This review included interventions provided to women who are pregnant, or planning a pregnancy, and post-partum mothers and their children aged 0-5 years.

Interventions to promote an optimal dietary vitamin D intake included:

- Vitamin D supplementation
- dietary advice/counselling/education on vitamin D
- intervention to deliver the above dietary advice/counselling/education about vitamin D to mothers, and others, with responsibility for feeding infants and young children in a range of childcare settings
- intervention to improve nutritional knowledge of vitamin D among parents and practitioners
- intervention to improve access of families with infants to food sources rich in vitamin D pre-cursors
- intervention to improve compliance with nutritional advice
- any interventions or practices other than supplementation which may affect vitamin D status in at-risk groups, for example
  - peer support
  - psychosocial interventions such as self-assertiveness skills to improve healthy eating
  - approach which aims to balance the need for safe exposure to sunlight against the risk of skin cancer
- media campaign
- Corroborative evidence related to the process and the context of the interventions, such as the components: development, content, structure,

setting, mode of delivery, acceptability, characteristics of the intervener and recipient, and any unintended harmful effects of the intervention were considered.

The review included all public health type interventions that can be delivered by practitioners at the primary care level and in the broader community. In addition, some of the interventions may be carried out by mothers, fathers and carers of infants and young children.

4.3 Outcomes of interest

4.3.1 Primary outcomes

Mothers

- Vitamin D intake
- Serum vitamin D concentration (25-hydroxy vitamin D [25 OHD])
- Incidence of osteomalacia

Infants aged 0-5 years

- Vitamin D intake
- Serum vitamin D concentration (25-hydroxy vitamin D [25 OHD])
- Bone mineral content and bone mineral density
- Incidence of rickets

4.3.2 Secondary Outcomes

- Changes in maternal body weight during prenatal, pregnancy and post-natal periods
- Changes in infant birth weight and body weight after birth
- Changes in numbers of hospital admissions (eg with rickets or osteomalacia)

4.3.3 Process measures of the intervention

- Uptake of intervention
- Compliance with intervention
- Changes in knowledge base of vitamin D
- Changes in practices (dietary/behavioural modification)
- Acceptability and sustainability (identification of effective components such as the development, setting and delivery of the intervention)

4.3.4 Cost or economic data

Outcomes considered were:

- Cost
- Cost per relevant effect
- Cost per QALY
- Net benefit

As no studies fulfilled the inclusion criteria for economic evaluation, the headings of effects (above) are theoretical, in the sense that these are the costs and effects that would have been relevant for studies that could have been found. The section on cost effectiveness in the results identifies a later study by Zipitis et al on vitamin D that was published after the cut off for the rest of this study. This study was used as the basis for modelling work.

4.4 Study types

A broad range of studies carried out in developed countries and evidence from UK were included:

- Systematic reviews*
- Randomised controlled trials (RCTs)

- Cohort studies (UK only)
- Control before and after studies (CBA)(UK only)
- Before and after studies (BA)(UK only)
- Interrupted time series studies (UK only)
- Case-control studies (UK only)
- Case series (UK only)

*(*In order to clarify details of the interventions, populations, outcome measures and follow-up time, the one eligible review identified was unpicked to individual studies.)*

The following types of studies were excluded:

- Primary studies set in developing or low income countries
- When sufficient high quality, up to date evidence was found for a specific question, older studies and/or those using weaker designs were not examined
- Papers in a language other than English
- Papers not held at the British Library
- Abstracts
- Evidence not related specifically to vitamin D

5 Methodology

A systematic review was conducted. A range of databases were searched from 1966 to 2006, using a sensitive strategy that combined relevant terms relating to pre-conceptual, pregnant and post-partum women, and children with appropriate vitamin D terms. The search was not limited by study type; but was restricted to studies in developed countries and in the English language only. We also checked reference lists of identified articles.

5.1 Literature search

The search strategy was developed at the NCC-WCH (as agreed by the NICE CPHE Secretariat) and the following databases were searched:

Completed and Ongoing Reviews

Cochrane Library: Cochrane Database of Systematic Reviews

DARE <http://www.york.ac.uk/inst/crd>

National Research Register (including CRD Ongoing Reviews) <http://www.update-software.com/National/>

Health Technology Assessment Database <http://www.york.ac.uk/inst/crd>

SIGN Guidelines http://www.sign.ac.uk

National Guideline Clearinghouse http://www.ahcpr.gov/clinic/assess.htm

National Coordinating Centre for Health Technology Assessment <http://www.hta.nhsweb.nhs.uk>

NICE web pages (published appraisals) <http://www.nice.org.uk/nice-web/>

Indexes to and summaries of Clinical Effectiveness Sources Including Reviews, Appraisals of Reviews, and Evidence Based Guidelines.

TRIP <http://www.tripdatabase.com>

Clinical Evidence http://www.clinicalevidence.com/ceweb/conditions/index.jsp

Health Evidence Bulletins Wales <http://www.uwcm.ac.uk/uwcm/lb/pep>

Searches for ongoing trials - conducted by agreement with the NICE team.

CCTR (Cochrane Library)

Controlled Clinical Trials (<http://controlled-trials.com>)

Bibliographic databases

AMED

EMBASE

CINAHL

MEDLINE

MIDIRS

PSYCINFO

Internet searches were also carried out using specialist and general search engines:

- specialist search engines, such as OMNI (http://www.omni.ac.uk);
- general search engines, such as Google (http://www.google.co.uk); and
- meta-search engines, such as Copernic (http://www.copernic.com).

5.2 Selection of studies for inclusion

The search included all types of primary studies in the English language, based on the inclusion criteria for participants, interventions and outcomes (See Section 5) using the above databases. We also checked reference lists of identified articles and background papers. For economic evaluations, all of the databases above were searched as well as NHS EED and HEED.

5.3 Exclusions

- Primary studies set in developing or low income countries
- If sufficient high quality, up to date evidence is found for a specific question, older studies and/or those using weaker designs will not be examined
- Papers in a language other than English
- Papers not held at the British Library
- Abstracts
- Evidence not related specifically to vitamin D

To ensure that all relevant studies were captured, a sensitive and comprehensive strategy was developed and adapted for different databases (see Appendix 1). We liaised with other organisations (the Centre for Reviews and Dissemination [CRD], and the Maternal and Child Nutrition Public Health Collaborating Centre at the University of York), working on literature-searching tasks, to ensure consistency across the search strategies and refine searches in accordance with the wishes of the NICE public health programme team.

5.4 Data extraction

Data were extracted and entered into evidence tables by one reviewer. Any discrepancies were resolved by discussion with another reviewer at the NCC-WCH.

5.5 Quality appraisal

Quality assessment was conducted by one reviewer. In cases where there was uncertainty, a second reviewer from the NCC-WCH was asked to appraise the evidence independently. The appraisal was carried out according to the guidance set out in the *Methods for development of NICE public health guidance manual – version 1.* (NICE. 2006)

5.6 Evidence level and grading

The evidence was graded according to guidance in the *Methods for development of NICE public health guidance manual – version 1.* (NICE. 2006) (Appendix 2)

6 Results

Due to the lack of relevant studies identified within the initial search period criteria (1990-2006), the criteria was extended to 1966-2006, using a very sensitive and comprehensive search strategy developed at the NCC-WCH. Reference lists from included studies and background papers were checked for potentially eligible studies not captured in the electronic search. It is possible, though unlikely, that important relevant studies published during this search period were missed.

The search strategy identified 4691 potentially eligible reports (4647 from electronic searches and 44 from bibliographic search of reference lists of included studies), of which 207 papers were retrieved for further examination. After full text review, 22 papers reporting on 17 studies, conducted between 1976 and 2004, met the inclusion criteria and were included in this review (see Appendix 3). Fifteen of the included studies were published before 1990 and two were published after 2000.

Included papers and methodological ratings

	Stand alone vitamin D supplementation	**Methodology checklist ratings**
	UK studies	
1	Brooke OG, Brown IR, Bone CD *et al.* Vitamin D supplements in pregnant Asian women: effects on calcium status and fetal growth. *British Medical Journal* 1980; 280:(6216)751-4. Maxwell JD, Ang L, Brooke OG, Brown IR. Vitamin D supplements enhance weight gain and nutritional status in pregnant Asians. *Br J Obstet Gynaecol* 1981; 88(10):987-91. Brooke OG, Butters F, and Wood C. Intrauterine vitamin D nutrition and postnatal growth in Asian infants. *British Medical Journal* 1981; 283:1024.	1+
2	Stephens WP, Klimiuk PS, Berry JL *et al*. Annual high-dose vitamin D prophylaxis in Asian immigrants. *Lancet* 1981; 2 :(8257)1199-202.	1-
3	Cockburn F, Belton NR, and Purvis RJ. Maternal vitamin D intake and mineral metabolism in mothers and their newborn infants. *British Medical Journal* 1980; 281:(6232)11-4.	2+
4	Pietrek J, Preece MA, Windo J *et al.* Prevention of vitamin-D deficiency in Asians. *Lancet* 1976; 1:(7970)1145-8.	2-
5	Congdon P, Horsman A, and Kirby PA. Mineral content of the forearms of babies born to Asian and white mothers. *British Medical Journal* 1983; 286:(6373)1233-5.	2–
6	Datta S, Alfaham M, Davies DP *et al.* Vitamin D deficiency in pregnant women from a non-European ethnic minority population--an interventional study. *BJOG: an International Journal of Obstetrics and*	2+

	Gynaecology 2002; 109:(8)905-8.	
	European studies	
7	Mallet E, Gugi B, Brunelle P *et al.* Vitamin D supplementation in pregnancy: a controlled trial of two methods. *Obstetrics and Gynecology* 1986; 68:(3)300-4.	1+
8	Delvin EE, Salle BL, Glorieux FH *et al.* Vitamin D supplementation during pregnancy: effect on neonatal calcium homeostasis. *Journal of Pediatrics* 1986; 109:(2)328-34.	1+
9	Ala-Houhala M. 25-Hydroxyvitamin D levels during breast-feeding with or without maternal or infantile supplementation of vitamin D. *Journal of Pediatric Gastroenterology and Nutrition* 1985; 4:(2)220-6.	1-
	US studies	
10	Hollis BW and Wagner CL. Vitamin D requirements during lactation: high-dose maternal supplementation as therapy to prevent hypovitaminosis D for both the mother and the nursing infant. *American Journal of Clinical Nutrition* 2004; 80:(6 Suppl)1752S-8S.	1-
11	Greer FR and Marshall S. Bone mineral content, serum vitamin D metabolite concentrations, and ultraviolet B light exposure in infants fed human milk with and without vitamin D2 supplements. *Journal of Pediatrics* 1989; 114:(2)204-12.	1+
12	Greer FR, Searcy JE, and Levin RS. Bone mineral content and serum 25-hydroxyvitamin D concentration in breast-fed infants with and without supplemental vitamin D. *Journal of Pediatrics* 1981; 98:(5)696-701. Greer FR, Searcy JE, Levin RS *et al.* Bone mineral content and serum 25-hydroxyvitamin D concentrations in breast-fed infants with and without supplemental vitamin D: one-year follow-up. *Journal of Pediatrics* 1982; 100:(6)919-22.	1+
	Vitamin D Health education programmes	
13	Henderson JB. A health education campaign to prevent osteomalacia in Asian women in Glasgow; 1984-86. *Journal of Human Nutrition and Dietetics* 1989; 2:(4)237-49.	2–
14	Dunnigan MG, Glekin BM, Henderson JB *et al.* Prevention of rickets in Asian children: assessment of	2–

	the Glasgow campaign. *British Medical Journal Clinical Research Ed.* 1985; 291:(6490)239-42. Dunnigan MG, McIntosh WB, Sutherland GR *et al.* Policy for prevention of Asian rickets in Britain: a preliminary assessment of the Glasgow rickets campaign. *British Medical Journal Clinical Research Ed.* 1981; 282:(6261)357-60.	
15	Save the Children Fund. Stop rickets campaign; report of a health education campaign published by the Save the Children Fund on behalf of the DHSS Asian Working Group. London: Save the Children Fund on behalf of the DHSS Asian Working Group; 1983.	2–
16	Stephens WP, Klimiuk PS, Warrington S *et al.* Observations on the natural history of vitamin D deficiency amongst Asian immigrants. *Quarterly Journal of Medicine* 1982; 51:(202)171-88. Stephens WP, Klimiuk PS, Warrington S. Preventing vitamin D deficiency in immigrants: is encouragement enough? *Lancet*. 1981; 25;1(8226):945-6.	2–
17	Box V. Rickets; what should the health education message be? *Health Visitor* 1983; 56:(4)131-4.	1–

6.1 Stand alone vitamin D supplementation

Seven "+" quality studies were identified which considered stand alone vitamin D supplementation (Brooke et al. 1980; Brooke et al. 1981; Maxwell et al. 1981; Cockburn et al. 1980; Datta et al. 2002; Mallet et al. 1986; Delvin et al. 1986; Greer & Marshall, 1989; Greer et al. 1981 & 1982;). All identified studies showed that antenatal vitamin D supplementation is effective in improving the vitamin D status of Asian and Caucasian women at delivery. Maternal serum 25 OHD concentrations (25 hydroxy vitamin D) were consistently higher in women supplemented with vitamin D during pregnancy compared to those with no supplementation. No adverse effects were reported.

6.1.1 Studies in the UK

Six UK based studies were identified (Brooke et al. 1980; Brooke et al 1981; Maxwell et al. 1981; Cockburn et al. 1980;Congdon et al. 1983;Datta et al. 2002; Pietrek et al. 1976;Stephens et al. 1981a) which assessed the effectiveness of stand alone vitamin D supplementation in the prevention of vitamin D deficiency among Asian and Caucasian populations. The evidence can be considered applicable and generalisable to the UK populations, depending on the regions, due to the difference in latitudes and amount of sunlight hours experienced. With the exception of one intervention (Datta et al 2002), all identified studies were conducted in the 1970s or early 1980s. Three of the studies (Stephens et al. 1981a, Congdon et al. 1983, Pietrek et al 1976) were considered poorer quality.

One RCT (Brooke et al. 1980; Brooke et al 1981;Maxwell et al. 1981)(1+), conducted in London (51.5º N) and which formed part of a systematic review (Mahomed et al. 2000), compared biochemical measurements and the mean weight gain of pregnant UK Asian women given high dose vitamin D supplements (25 ug/day) (n=59) or placebo (n=67) during the third trimester. Postnatal vitamin supplements were not routinely given (Brooke et al. 1981). The results suggest that vitamin D supplements to Asian infants prenatally would improve their physical growth in terms of weight and height gains. The authors reported a significant increase in maternal plasma 25 OHD levels (nmol/l) in the supplemented group, when compared with the placebo group at term (168 ± 96.0 vs. 16.2 ± 22.1), and in maternal mean daily weight gain (g) in the last trimester in the supplemented group, when compared with the placebo group (63.3 ± 20.70 vs. 46.4 ± 29.50). This mean weight gain in supplemented mothers was near to the quoted average weight gain for European women in their last trimester. Mean infant birth weight (g) was higher in the supplemented group than in the placebo group, but the difference was not significant (3157 ± 468.5 vs. 3034 ± 523.9). There was no documented report of adverse events. The infants of these two groups were followed up for one year after the trial. There was a significant increase in mean weight (kg) in infants whose mothers received antenatal vitamin D supplements (n=53), when compared with infants receiving no antenatal vitamin D supplements (n=64) at three, six, nine and twelve months, resulting in a significant incremental increase in weight over the 12 months (6.39 ± 0.78 vs. 5.92 ± 0.92).

A non-RCT (Cockburn et al. 1980)(2+) conducted in Edinburgh (55.7º N) suggests vitamin D supplementation (10ug/day) given to women (ethnicity unknown) from the 12th week of pregnancy may be beneficial. The authors reported significant increases in maternal plasma 25 OHD concentrations (nmol/l) between the supplemented group (n=82) and the placebo group (n=82) at the 24th week (39 vs. 32.5, $p<0.01$), 34th week (44.5 vs. 38.5, $p<0.05$) and at delivery (42.8 vs. 32.5, $p<0.001$). A significant increase in 25 OHD concentrations was also reported in infants of supplemented women (vitamin D group: 34.5 [n=54] vs. placebo group; 20.3 [n=86], $p<0.001$) at day six. Formula-fed infants had significantly higher 25 OHD concentrations ($p<0.01$) than breast-fed infants, supplemented or unsupplemented at day six. There was a highly significant correlation between maternal and cord values at delivery (r=0.71). There was no documented report of adverse events.

A before and after study (Datta et al. 2002)(2+), among pregnant women from ethnic minorities (n=160, African, African-Caribbean, Asian, far-Eastern, Middle Eastern) living in Cardiff (51.5º N), assessed the effect of vitamin D supplementation at the first antenatal visit. Fifty percent of women were found to have low vitamin D levels (plasma 25 (OH) D <20nmol/l) and were given vitamin D supplements (20-40 ug/day). At delivery, the mean level of vitamin D had increased from 15 nmol/l at booking to 27.5 nmol/l at delivery, suggesting that biochemical screening and subsequent supplementation would be appropriate in similar populations.

A poorer quality non-RCT (Pietrek et al. 1976) (2-) in Glasgow (55.9º N) compared biochemical measurements in Asian families, given vitamin D supplements (n=18 members from four families) (75 ug/week) or provided with vitamin D fortified chapatti flour (150 ug/kg)(n=32 members from six families), and a control group given no vitamin D (n=16 members from four families). There was a significant increase in serum 25 OHD concentrations in the weekly vitamin

D group and in the fortified group when compared with the control group at three and six months. The number of biochemical abnormalities suggestive of rickets was also reduced (two in control group vs. one in weekly vitamin D group vs. 0 in fortified flour group). No adverse events were documented.

A poorer quality RCT (Stephens et al. 1981a) (1-), among Asian women living in Rochdale (53.6º N), compared the effects of a single dose of vitamin D given orally (2500 ug) or intramuscularly. The results suggest that both oral and IM vitamin D given every six months are equally effective as a prophylactic measure. The authors reported a significant increase in serum 25 OHD concentrations (nmol/l) one month after treatment in the oral supplementation group (n=12) when compared with the IM group (n=12) (52.5 ± 12.0 vs. 32.5 ± 13.8. No significant differences were observed between the two groups at three months and five months after treatment. Both the oral and the IM groups achieved a significantly higher serum 25 OHD concentration, at five months than at baseline (8.00, 95% CI 2.33 to 13.67 and 9.50, 95% CI 1.75 to 17.25 respectively). The range of values produced by oral vitamin D was much less than the range produced by IM vitamin D (mean 24.5, range 19.3 -34.3 nmol vs. mean 23.5, range 12.8–52.3). At one year after the study, every patient had a serum 25 OHD level >12.5 nmol/l. There was no documented report of adverse events.

A poor quality cohort study (Congdon et al. 1983)(2-), conducted in Leeds (53.5º N), compared biochemical and bone mineral measurements of babies born to Asian women deficient in vitamin D (n=45, group 1), to Asian women supplemented with vitamin D (25 ug/day) during the 3rd trimester of pregnancy (n=19, group 2) and to white women (n=12, group 3). There was a significant difference in cord blood 25 OHD concentrations between Asian babies who received antenatal supplementation and Asian babies who did not. The proportion of plasma 25 OHD concentrations below 10nmol/l (associated with osteomalacia) was 91% in the unsupplemented group, 58% in the supplemented group and 0% in the white mothers. At term, babies born to mothers deficient in vitamin D, had significantly lower cord blood 25 OHD concentrations (nmol/l) when compared with babies born to white women (5.90 ± 0.94 vs. 33.40 ± 3.60, p<0.001). Asian babies whose mothers had been supplemented with vitamin D, also had significantly lower cord blood 25 OHD concentrations than babies in group 3 (15.20 ± 3.15 vs. 33.40 ± 3.60, p<0.001) at term. There was no significant difference in the babies birth weight or bone mineral content within the first five days after birth. There was no report of breastfeeding status of the infants studied. There was no documented report of adverse events.

6.1.2 Studies in Europe

Three RCTs were identified which were conducted in Europe between 1985 and 1986, of which two were considered "+" quality (Delvin et al. 1986;Mallet et al. 1986) and one "-" quality (Ala-Houhala 1985). The studies only included Caucasian populations and may not be applicable and generalisable to the UK populations due to the difference in latitudes, ethnicity, sunlight hours experienced and the food fortification policy of various countries. The dosage of vitamin D supplements recommended differed from that by COMA in the UK.

The first RCT (Delvin et al. 1986) (1+) in Lyons (45.7º N), compared the effects of vitamin D supplements (25 ug/day) given to women (ethnicity unknown) in the 3rd trimester (n=40) with no vitamin D supplement(n=40). The authors reported significantly higher serum 25 OHD concentrations (ng/ml) in the supplemented group than the control group (26 ± 7 vs. 13.8 ± 8) at delivery (June), and in (breastfed) infants at day four (13 ± 1 vs. 5 ± 1). There was no reported difference in infant birth weights (details not presented). There was no documented report of adverse effects.

The second RCT (Mallet et al. 1986)(1+)(part of a systematic review, Mahomed et al. 2000), was conducted in Rouen (49.4º N). Caucasian pregnant women were either supplemented with antenatal vitamin D (n=21) (25 ug/day) in the 3rd trimester, or given a single dose of vitamin D (5mg) (n=27) in the 7th month of their pregnancy, or given no vitamin D supplement (n=29). The authors reported a significant increase in maternal serum 25 OHD concentrations (nmol/l) in the daily dose group, compared with the control group (25.3 ± 7.7 vs. 9.4 ± 4.9), and in the single dose group compared with the control group (26.0 ± 6.4 vs. 9.4 ± 4.9) at delivery. There was a positive correlation between the maternal and cord blood 25 OHD concentrations (r=9.5, p< 0.0001). There was no significant difference in the mean infant birth weight (g) between the three groups

The third, poorer quality RCT (Ala-Houhala. 1985)(1-), conducted in Finland (61º N), considered the effects of maternal and infantile vitamin D supplementation among infants who were breastfed. Around half the mother-infant pairs were studied in winter and half in summer. The 92 pairs were randomized to three groups: group 1 where mothers were supplemented with vitamin D after delivery (25 ug/day) (n=27), group 2 where infants were supplemented with 10ug vitamin D per day (n=31) or group 3 where infants were supplemented with 25ug vitamin D per day (n=29). During pregnancy, all the mothers had received vitamin supplementation (0-12.5 ug/day). At delivery, maternal serum 25 OHD levels were significantly higher (all absolute data presented graphically) in all three groups of women (p<0.001 in groups 1 and 2; p<0.01 in group 3). At eight weeks after delivery (in winter), the levels were significantly higher in group 1 than in group 2 and 3 (p< 0.001) but there were no such difference between group 1 and group 3 in summer. The infantile levels at delivery were similar in all three groups in winter but were significantly lower in group 3 than in group 1 (p<0.05) in summer. In winter, at the age of eight weeks, levels in group 1 infants were significantly lower than those in groups 2 and 3 (p<0.001). In summer, serum 25 OHD levels of group 1 infants were similar to those in group 2, but were significantly lower than those in group 3 (p<0.001). Throughout the study, there was no signs of clinical or biochemical rickets seen in the infants with 25 OHD levels below the risk limit for rickets. There was no documented report of adverse events.

6.1.3 Studies in the US

Three RCTs were identified which were conducted among predominantly Caucasian populations in the US between 1980 and 2004, of which two (Greer et al. 1981;Greer et al. 1989;) were considered "+" quality and one (Hollis et al. 2004) was considered "-" quality. The evidence may not be applicable and generalisable to the UK populations due to the difference in latitudes, ethnicity, amount of sunlight hours experienced and the food fortification policy of the two countries. The dosage of vitamin D supplements recommended differed from that by COMA in the UK.

The small RCT (Greer et al. 1989)(EL 1+) conducted in Massachusetts, (42.4º N), compared bone mineral content (BMC) and biochemical measurements in exclusively breast-fed infants (n=46, 13 born in summer, 33 in winter) given 10ug /day vitamin D (n=22, group 1) and infants given a daily placebo (n=24, group 2) within the first week of delivery. All infants had white mothers who also received supplemental vitamin D during pregnancy. An additional convenience sample of healthy exclusively formula-fed infants (n=12, group 3) was also included as a comparison group. Maternal mean vitamin D intake (IU/day) of groups 1 and 2 did not differ between groups 1 and 2. Serum 25 OHD concentrations (ng/ml) did not differ at birth among the three groups. However, they were significantly higher in group 1 than in groups 2 and 3 at six weeks (30.25 ± 9.54 vs. 15.76 ± 9.81 vs. 30.21 ± 6.08), at three months (38.89 ± 10.34 vs. 15.72 ± 11.25 vs. 37.24 ± 6.08) and at six months (36.96 ± 11.86 vs. 23.53 ± 9.9.4 vs. 37.57 ±8.54). All three groups had an increase in BMC. The measured BMC (mg/cm) in group 2 was significantly higher than group 1 (101 ± 17.9 vs. 89.5 ± 12.5, $p<0.05$) at six months. Formula-fed infants in group 3 had a significantly higher change in measured BMC than that of combined group 1 and 2 (38.8 ± 24.3 vs. 9.2 ± 13.2 vs. 18.0 ± 18.2) at six months. There was no significant difference in mean body weight (g) between the three groups during the study (7570 ± 858 in group 1 vs. 7752 ± 1182 in group 2 vs. 7633 ± 1002 in group 3). There was no documented report of adverse events.

A small RCT (Greer et al. 1981)(1+), conducted in Ohio (40.1º N), compared the effects of supplemental vitamin D in exclusively breast-fed infants (n=18, 16 born in summer and two in winter) between the 1st and 2nd weeks after birth. The authors reported no significant difference in bone mineral content (BMC) between the group given 10ug/day vitamin D (n=9) and a placebo group (n=9) at six weeks, but a significant increase in BMC in the supplemented group at 12 weeks ($p<0.003$). Comparison between the supplemented infants with an additional convenience sample of formula-fed infants (n=12) showed a significant higher BMC in the supplemented group at six weeks ($p<0.03$) but not at 12 weeks. Serum 25 OHD concentrations (ng/ml) were significantly higher in the supplemented group than the placebo group (38 vs. 20, $p<0.01$) at 12 weeks. Mean maternal vitamin D intakes (assessed by dietary recall) were similar in the two groups during the study. There was no documented report of adverse events.

A poorer quality RCT (Hollis et al. 2004) (1-), conducted in South Carolina (32.8º N), compared the effects of high-dose maternal vitamin D supplementation in breastfeeding women within one month after delivery, and their infants, who also acted as their own control group. The authors reported a significant increase in total circulating serum 25 OHD concentrations (ng/ml) in women receiving 50ug/day vitamin D (group 1, n=9 [(3 African Americans]) (27.6 ± 3.3 vs. 36.1 ± 2.3) and in women receiving 100ug /day vitamin D (group 2, n=9 [2 African Americans]) 32.9 ± 2.4 vs. 44.5 ± 3.9) from baseline to three months. There was a significant increase in total circulating serum 25 OHD concentrations in nursing infants in both groups. There were no data on the effect of seasonal variation. There was no documented report of adverse events.

6.1.4 Cost-effectiveness

A literature search did not identify any relevant literature addressing the cost-effectiveness of public health interventions in promoting an optimal dietary Vitamin D intake or promoting advice and/or increased uptake of vitamin D

supplementation. Subsequent to this search a paper was identified which, whilst not a formal economic evaluation, implicitly addressed the cost-effectiveness of vitamin D supplementation in a UK setting with a large Asian community (Zipitis et al. 2006: see appendix for list of excluded references). A cost analysis suggested that the cost of vitamin D supplementation in children, as primary prevention, could be cost saving when targeted at the higher risk Asian population. This finding was based on the costs of vitamin D supplementation using the dose recommended by COMA set against the cost of treating vitamin D deficient children in the absence of any supplementation.
A health economic model was developed from this study with the intention that it could inform recommendations based on health economic considerations. However, it was ultimately felt that such a model was not useful due to important gaps in the clinical evidence concerning the effects of vitamin D supplementation.

6.2 Effectiveness of interventions to promote optimal dietary intake of vitamin D

The literature search (1990 to 2006) did not identify any studies, which evaluated the effectiveness of interventions to promote optimal dietary intake of vitamin D, nor any published intervention programmes which aimed to promote optimal uptake of vitamin D, in the UK or other developed countries. Expanding the search back to 1966, five intervention programmes were identified (Box, 1983, Dunnigan et al. 1981;Dunnigan et al. 1985;Henderson. 1989;Save the Children Fund. 1983;Stephens et al. 1982;Stephens et al. 1981b), all of which were carried out in the UK between 1979 and 1989. The quality of reporting in these studies is poor and insufficient details are provided. The studies tend to provide very limited information on how the intervention was planned and delivered. As a result, all are classified as “-“quality. The target populations in these studies included Asians of all ages (Adults 19-70 years and children 0-18 years).

An uncontrolled before-and-after study (Dunnigan et al. 1981;Dunnigan et al. 1985) (2-) evaluated the outcomes of the Glasgow Rickets Campaign which comprised a package of health education with free vitamin D supplements (dose unknown) to Asian children (aged 0-18 years) in Glasgow (55.9 º N), lasting 12 months. The intervention was supervised by a Working group and delivered by community health professionals who received in-service training, working closely with the Asian community via newsletters, posters, radio, cartoons and at meetings.

A significant rise was reported in the serum 25-OHD concentration (nmol/l) (15.5, 95% CI 4.5 to 55.0 before vs. 21.0, 95% CI 6.8 to 67.5 after campaign, $p< 0.007$) among 59 paired samples (aged 5-17 years) at three years. It is not clear if these 'matched pairs' were initially randomly selected. There was a significant reduction in the number of cases (age not reported) in the severe 'rachitic' category (6% before vs. 2% after the campaign, $p<0.05$) but no significant difference in the prevalence of abnormal X-ray appearances (12% vs. 7.5%) among the children (age not reported). The number of children discharged from hospital with nutritional rickets decreased after the campaign (3 vs. 2 in the 0-4 age group and 13 vs. 9 in the 5-16 age group). The study also reported an increase in the mean daily doses of vitamin D supplement (10ug) dispensed to Asian children through clinics, health centres and schools (2200 before vs. 3300 doses after the campaign).

Another uncontrolled before-and-after study (Henderson. 1989)(2-) evaluated the outcomes of the Glasgow Rickets campaign, a health education campaign which comprised a package of health education with the sale of vitamin D supplements (dose unknown) at cost price, to Asian women (aged 17-60 years) in Glasgow (55.9 º N) lasting 12 to 24 months. This campaign followed the experience of the previous Glasgow rickets campaign for Asian children. (Dunnigan et al. 1981;Dunnigan et al. 1985). The intervention was delivered by Asian link workers who visited homes of Asian families to give information about osteomalacia and offered sales of vitamin D supplements at cost price. Similar to the rickets campaign for children, this intervention was supervised by a Working

group, and there was close involvement with health professionals and the Asian communities. Information leaflets in English and Asian languages were distributed to women at homes, clinics or temples. The materials were not piloted prior to the launch of the campaign.
A significant decrease was reported in the serum 25-OHD concentration (nmol/l) (28.0, 95% CI 10.0 to 79.0 before vs. 21.0, 95% CI 8.0 to 55.0 after campaign, $p < 0.003$) among 59 paired samples (aged 23─60 years) at 18 months. It is not clear if these 'matched pairs' were initially randomly selected. In this group, there was no significant difference in the prevalence of severe vitamin D deficiency and potential osteomalacia (as defined by serum 25 OHD levels below 12.5nmol/l) before and after the campaign (10% vs. 12%). Questionnaire surveys of the women showed that the number of women taking vitamin D supplements decreased from 59% three months after the campaign to 19% nine months after the campaign (when home visits stopped due to expired funding). Over 80% of the women made no attempt to purchase further supplies and the reasons given being 'not interested', 'feel no different' and 'weight gain'. There was considerable apathy from the general practitioners (n=500, response rate 38%) with only 27% indicating a desire for more information. Only 3% of GPs surveyed prescribed vitamin D for Asian women.

An uncontrolled (2-) health education campaign by a charity organisation and voluntary Asian groups (with UK government support) was identified which aimed to prevent vitamin D deficiency in twenty five area Health Authorities (Save the Children Fund, 1983). The campaign comprised information that vitamin D was essential to prevent rickets and osteomalacia, and that it can be obtained from sunlight, diet and supplements. The vitamin D supplements policy was left to the individual health authorities to decide. The culturally sensitive campaign used formal and informal channels of communication with the local Asian communities and the key messages were disseminated via the Asian media. Asian liaison workers acted as a link between health professionals and the community in order to reach large audiences and 'hard to reach' groups

Evaluation of the campaign was carried out immediately after the campaign and at 12 months after the campaign using a piloted questionnaire by interviewers fluent in English and Asian language(s). The questionnaire assessed knowledge in five categories related to rickets and vitamin D. Pre-campaign data were available for the control group but not for the experimental groups, and post-campaign data were available for the experimental groups but not the control group. It is not clear if the samples were randomly selected in the respective areas. The results suggest there was a significant increase in mean knowledge scores immediately after the campaign (n=217) and 12 months after the campaign (n=127) compared to before the campaign (n=87) and in total group score (73% and 58% vs. 29%, respectively p<0.01).
There were reports of initial rise in supplement uptake (16% in Liverpool and 11.3% in Birmingham and 17% in the early quarter following the campaign) but the level dropped to the pre-campaign level over the next quarter. However, these data were obtained from health clinics dispensing vitamin supplements; data on vitamin D supplements obtained from the chemist and GPs was unavailable. There was no evaluation on the incidence of rickets after the campaign.

An uncontrolled study (Stephens et al. 1981b;Stephens et al. 1982) (2-) compared two surveys of the prevalence of rickets and osteomalacia in Rochdale (53.6ºN) in 1970 and in 1980. Between the survey dates, a health education campaign took place in Rochdale to alert the community and its medical advisers to the problem of vitamin D deficiency. Through posters, leaflets and personal contact via health visitors and community leaders the campaign encouraged adequate exposure to sunshine and increased consumption of foods containing vitamin D. The available information on the campaign was insufficient to assess the reliability and validity of the outcomes measured. A comparison was made between the survey data of self-referred Asians in 1970 (n=178, 112 adults, 66 children) and in 1980 (n=262, 159 adults, 103 children). The 1980 group included 69 Asians who were randomly selected.

Among Asian children (aged five to 18 years), there was a significant difference in height below the 50th centile in children in 1970 compared to children in 1980 (60% vs. 45%, $p<0.005$). There was also a significant difference in mean daily dietary vitamin D intake (ug/day) between the two groups (1.93 ± 1.05 [n=58] in 1970: vs.: 2.67 ± 1.68 [n=103] in 1980; $p<0.01$). The proportion of Asian children taking regular vitamin D supplements was 9% in 1970 versus 13% in 1980. The number of admissions to hospitals with diagnosis of rickets was 30 in 1970 and two in 1980. It is not possible to ascertain whether these findings were due to the campaign. Among Asian adults (aged 18 to over 70 years), there was no significant difference in mean dietary vitamin D intake between 1970 and 1980 (Stephens et al. 1981b) (2-). The proportion of Asian adults taking regular vitamin D supplements was 0% in 1970 versus 3% in 1980. It is not possible to ascertain whether these findings were due to the campaign.

One small quasi-RCT (Box. 1983) (1-), a pilot study conducted in London (51.5º N), evaluated the effects of a dietary advice to Asian pregnant women early in their pregnancy. The intervention was delivered by a health visitor at the antenatal clinic and included advice and counselling to increase dietary vitamin D content and exposure to sunlight. Interpreters were available when required during the intervention. The authors reported a significant increase in mean dietary vitamin D intake (mg/day) in the counselled group (n=11) when compared with the non-counselled group (n=9) at 4 months (a mean increase from baseline of 1.5 ± 1.2 versus 0.4 ± 0.5, $p< 0.05$). However, the mean increase from baseline in serum 25 OHD levels (ng/ml) was significantly lower in the counselled group than the non-counselled group at 4 months (0.07 ± 0.06 vs. 0.15 ± 0.07, p~ 0.02). The author suggested that the unexpected results could be due to confounders such as reliability of self-reported data on dietary vitamin D intake and difference in sunlight exposure in the two groups.

6.3 Sub-questions for studies

Where available, data on the included studies on promotion of vitamin D were extracted to address the following questions:

- What is the theoretical basis for the intervention?
- How does the structure and content of the intervention influence effectiveness?
- How does the way that the intervention is delivered influence effectiveness?
- Does effectiveness vary by age, gender, ethnicity or the social/professional group of those delivering or receiving the intervention?
- Does training, skill development and funding of potential deliverers influence effectiveness?
- Does effectiveness vary with site/setting or intensity/duration of the intervention?
- What are the views of those receiving and delivering the intervention?
- What evidence is there on cost-effectiveness (in terms of money, people and time)?
- What evidence is there of unanticipated or harmful effects of the intervention?
- Are there barriers to replication of effective intervention?
- Specific issues will be considered when working with black and minority ethnic groups who are based predominantly in the home.

Table 7.1 Sub-questions for intervention studies to promote uptake of vitamin D supplementation

Reference	How do structure and content of intervention influence effectiveness	Does effectiveness vary by gender, age, ethnicity, religious practices, social/professional group receiving or delivering the intervention, including specific issues when working with predominantly home-based ethnic minority groups	Does effectiveness vary by site/setting or intensity/duration of intervention	What are the views of those receiving and delivering the intervention	Is there evidence of unintended or harmful effects reported	Are there barriers to replication of effective intervention
(Henderson 1989)	1. Supervision of campaign by the Rickets Working group to oversee/support the campaign 2. Co-ordination by an Asian (Muslim) supervisor and an co-ordinator with experience of the Glasgow rickets campaign for children (1979-1983) 3. Employment of 4 link workers who were Asian women from the Glasgow Asian community, one Muslim, two Sikhs and one Hindu, who could communicate in English and the appropriate Asian language 4. Information of the campaign to Community Health professionals in face-to-face presentations, discussions and explanatory leaflets; GPs were directly addressed by campaign co-ordinator 5. Involvement of Asian community with visits to Sikh and Hindu temples 6. After funding discontinued, Asian	1. Target population: Asian women aged 19 to 60 years (no details on social/professional group) 2. Delivered by Asian women link workers (no details on age or social/professional group) in Asian women's homes	1. Homes of women, Sikh or Hindu temples, health clinics and antenatal clinics 2. Explanatory and information leaflets in English, Guajarati, Hindi, Urdu and Punjabi to Asian women 3. The duration of the intervention was 24 months 4. No details on the intensity of the intervention	1. Asian women gave reasons for non-purchase of vit D supp as: 'not interested' 'feel no different', 'forgotten' and 'weight gain' 2. Health professionals reported low level of interest in the campaign 3. Health visitors concerned with Asian patients were discouraged by nursing	None known to be harmful reported	1. The funding of the campaign lasted for only 12 months, after which time the link workers withdrew home visits 2. Compliance Low priority on purchasing vit D supp when the women felt 'well', difficulties in remembering to take medications when well 3. Health professionals: low priorities by health visitors to campaign on women after previous

	supervisor continued to promote vit D supp uptake in health clinics and antenatal clinics			management to participate in giving their views on the campaign 4. No report on the campaign from the link workers		campaign on children, also Health visitors duties generally 'child-centred'. Lack of motivation amongst GPs towards preventive medicine in general in the face of may competing claims of general practice.
(Dunnigan et al. 1981;Dunnigan et al. 1985)	1. Formation of a multidisciplinary working group to oversee/support the campaign 2. In-service training provided for health professionals to prepare their role in the campaign, supported by fact sheets explaining the policy and clinical features of Asian rickets 3. Close involvement with the Asian community and Asian social and religious groups, including the Glasgow Community Relations Council in a series of meetings on Asian rickets, supported by a simple fact sheet to the Asian community	1. Target population: Asian children (aged 0-18 years) via their carers in the Asian communities 2. Delivered by community nurses, midwives, health visitors, dietitians, clinical medical officers and general practitioners (no details on their age, gender, ethnicity and religious practices) 3. No report of details of interventions relating to specific issues when working with minority ethnic groups 4. No report if Asian languages were used	1. Children attending Health Board clinics, health centres, 3 selected schools with a high proportion of Asian children 2. Asian communities: Asian social and religious groups, leaders of Asian communities, Glasgow Community Relations Council 3. Press articles for Asian Newspapers, community newsletters, cartoon 'In Place of the Sun' and stills, and posters displayed at Asian Meeting places. 4. The duration of the intervention was 12	Not reported	None known to be harmful reported	Not reported

		to communicate with the women or the Asian communities	months 5. No details on the intensity of the intervention			
(Save the Children Fund. 1983) Stop Rickets Campaign	1. Setting up of a Working Group on Rickets supported by the NHS and managed by the Save the Children Fund (SCF). 2 Appointment of a campaign Director who speaks 4 Asian languages she was supported by a secretary 3. A special campaign logo incorporating the 'sun and a spoon'. 4. Extensive networking to identify influential figures of local Asian communities including a register of Asian places of worship in launch areas. 5. Wide distribution of campaign materials to health professionals and to various national and local community organizations, community relations officers, explaining the aims and scope of the campaign. 6. Extensive use of media involvement with National and Asian press, radio and TV to promote the campaign. 7. Two radio jingles about vitamin D were introduced based on Hindi/Urdu folk rhymes: Regular showing of the film 'Growing Day by Day', posters in Asian shops and campaign leaflets in clinics, GP surgeries, temples and gurdwaras.	1. Target population: Asian communities in 25 AHAs 2. Delivered by campaign and health professionals, influential figures and local Asian community leaders, Asian liaison workers (no information on their age and gender) and the Asian media outlets	1. Delivered in homes, clinics, health centres, temples, gurdwara, factories, ESL classes, and via Asian TV, radios, cinemas (posters, songs and films in Asian languages) 2. The duration of the campaign was 2 years 3. No report of details on intensity of intervention	Not reported	None known to be harmful reported	1. Insufficient funding to evaluate results after campaign 2. Language and cultural barriers 3. Access to Asians outside home (fear of going outside home –street attacks and racial harassment) 3. Training of interpreters and liaison workers 4. NHS staff handicapped by their lack of awareness of the background and culture of their Asian clients 5. Lack of members from minorities among health professionals working in areas with substantial ethnic minorities

	8. Consultation and involvement with the community relations councils on local Asian communities and no of languages spoken; also consultation with area medical officers about campaign tactics 9. Three pilot launches 10. Strong ministerial backing 11. Campaign arrangements agreed between the authority and Asian community leaders 12. Formal meetings: visit by the Director and campaign staff to campaign areas. And briefing sessions to community health doctors, health visitors, school and district nurses, teachers and social workers, GPs. Visits to women's organisations, temples, mosques and gurdwaras supported by the Asian Leaders' Pack to explain the campaign, also visits to Asian employers and factories, ESL groups, antenatal and maternal and Child clinics 13. Informal meetings with Asian women self-help groups to identify unofficial 'opinion leaders' for their influence 14. Respect for Asian tradition, e.g. where there is objection to a woman speaking in a mosque made by senior members of the religious community, male doctors would give the talks and hold discussions. Care taken to avoid criticism of traditional Asian diets. 15. Taking feedback seriously from Asian mothers to develop a new leaflet 'Why You					

	Need Vitamin D' 16. Use of liaison workers					
(Stephens et al. 1982) Rochdale	Limited information available: 1. Distribution of posters, leaflets and personal contact via health visitors and community leaders 2. Advice to take supplemental vitamin D preparations on a regular basis was not included in the campaign 3. No selective food fortification was introduced	Limited information available: 1. Target population: Asian adults (19 -70+ years) and children (5 - 18 years) 2. Delivered by health visitors and community leaders (no information on their age, gender, ethnicity and religious practices) 3. No report of details of interventions relating to specific issues when working with minority ethnic groups	No details	Not reported	None known to be harmful reported	Not reported
(Box. 1983) London	4. Advice given: At 1st visit (6/8 weeks) Food sources rich in vitamin D Reinforce message with samples of food and proprietary brands Maximise exposure to sunlight Serum 25 OHD levels measured At 2nd /3rd visit (2/4 months) Women questioned about understanding of advice previously given Advice reinforced Serum 25 OHD levels measured at 3rd visit 2. Strategy Women encouraged to bring their mothers-in-law to clinic, as the latter usually make decision about the family's	1. Target population: Asian pregnant women 2.limited demographic information on the women who participated 3. Delivered by a non-Asian Health visitor 4. Use of Hindu, Muslim and Sikh-speaking receptionists as interpreters	1. Intervention delivered at antenatal clinic 2. Intervention given at 6/8 weeks and at two and four months	Counselling situation appeared to be much appreciated by the Asian women, particularly those who no longer had an extensive female network to advise them on pregnancy and lactation. The women felt compatible with the health visitor as they	None known to be harmful reported	1. Retention of knowledge 2. Affordability of fortified proprietary brands 3. Food preference (oil fish much disliked by the study population) 4. Reliability of answers: Asians culturally more likely to give 'desired' answers

	diet			returned on other occasions to talk about a range of pregnancy and other problems.		

6.4 Limitations of the evidence base

General issues

There is a dearth of up-to-date robust evidence to answer the research questions. Of the 17 studies identified, 15 were published during 1976-1989 and only two after 2000. Interpretation of available evidence and direct application of findings to the UK population should therefore be considered with caution. Variations in regional latitudes, sunlight exposure, ethnicity, culture, dietary and dress habits, language barriers, access to health care, food fortification policy and adherence to the public health advice on sun protection are likely to influence outcomes and compound the problem of vitamin D deficiency. Some of the identified health education programmes identified an increase in knowledge about rickets and uptake of supplements, but did not demonstrate an improvement in health outcomes. Furthermore, as many of the identified studies were uncontrolled it was not possible to assess the impact of “doing nothing” as spontaneous recovery has been reported to occur in vitamin D deficient Asian children over the summer months.

There are methodological shortcomings in some of the studies identified. For identified RCTs, methods of randomization and allocation concealment were not often reported and in some cases, sample size was small and there was insufficient information on compliance and drop-out rates, and the use of intention-to-treat analysis. Confounding bias common in quasi-RCT, non-RTCs, cohort and case series studies (all UK studies) might have influenced the results of these studies and they included factors such as sampling bias, dietary and dress habit, sunlight exposure, place of birth and duration of residence. Similar confounders could also influence the findings of the four UK health education intervention studies, which employed a before-and after study design (three of which had no control group).

Reporting of the process-related corroborative evidence of the health education interventions tended to be poor with little detail on the infrastructure, approaches, strategy and delivery mechanism of the interventions. In all the identified studies, there was no documented report of adverse events. It is unclear if adverse events did not occur or if they were not assessed as part of the outcomes.

6.5 Gaps in evidence

No studies were identified which aimed to improve the vitamin D status of women specifically at the pre-conceptual period, nor in women and children in low income households, nor did we identify any intervention studies which assessed the effect of sunlight exposure on the vitamin D status of women.

We did not identify any studies of good quality, which addressed the following:

- intervention to improve access of families with infants to food sources rich in vitamin D pre-cursors
- intervention to improve compliance with nutritional advice
- any interventions or practices other than supplementation which may affect vitamin D status in at-risk groups, for example
  - peer support
  - psychosocial interventions such as self-assertiveness skills to improve healthy eating
  - approach which aims to balance the need for safe exposure to sunlight against the risk of skin cancer
- Corroborative evidence related to the process and the context of the interventions, such as the components: development, content, structure, setting, mode of delivery, acceptability, characteristics of the intervener and recipient, and any unintended harmful effects

We did not identify any ongoing studies, which addressed the research questions of this review.

There is a lack of up-to-date robust evidence, both on the effects of vitamin D supplementation and of interventions to promote the optimal uptake of vitamin D supplements. The effect of vitamin D on infant bone mineral content remains uncertain. New studies would benefit from the improved methodological approach, developed in the last decade, in designing and evaluating complex public health interventions.

In considering the applicability and generalisability of the evidence reviewed, a cautious interpretation is needed, taking into account the paucity, in quantity, quality and currency, of available evidence and their validity in informing future public health policy in vitamin D supplementation in the UK.

7 Appendix

7.1 Appendix 1

Search Strategy

Searches for NICE Rapid Review 'The effectiveness and cost-effectiveness of interventions to promote an optimal intake of Vitamin D to improve the nutrition of preconceptional, pregnant and post-partum women and children'

The searches were initially carried out across the Medline, Embase, Cinahl, CCTR, CDSR, DARE and Amed bibliographic databases. A sensitive strategy that combined relevant terms relating to preconceptional, pregnant and post-partum women, and children up to five years of age with appropriate vitamin d terms was used, and focused on interventions rather than being restricted to outcomes. The search was not limited by study type; however, it was restricted to the English language and the years 1990-present.

Medline 1990-2006

1. exp PREGNANCY/
2. pregnan$.tw.
3. PRECONCEPTION CARE/
4. PRENATAL CARE/
5. POSTPARTUM PERIOD/
6. (pre?conception or pre?pregnan$ or pre?natal or ante?natal or post?partum or post?natal or puerperium or childbear$).tw.
7. or/1-6
8. INFANT, PREMATURE/
9. INFANT, POSTMATURE/
10. INFANT, LOW BIRTH WEIGHT/
11. (low adj birth adj weight).tw.
12. lbw.tw.
13. INFANT, VERY LOW BIRTH WEIGHT/
14. vlbw.tw.
15. INFANT, NEWBORN/
16. neonat$.tw.
17. newborn$.tw.
18. exp INFANT/
19. infan$.tw.

20. CHILD, PRESCHOOL/
21. (baby or babies).tw.
22. (child$ adj5 pre?school).tw.
23. toddler$.tw.
24. or/8-23
25. or/7,24
26. exp VITAMIN D/
27. vitamin d.tw.
28. alfacalcidol$.tw.
29. hydroxycholecalciferol$.tw.
30. dihydroxycholecalciferol$.tw.
31. calcifediol$.tw.
32. calcitriol$.tw.
33. (dihydroxyvitamin d or hydroxyvitamin d).tw.
34. dihydrotachysterol$.tw.
35. doxercalciferol$.tw.
36. ergocalciferol$.tw.
37. paricalcitol$.tw.
38. cholecalciferol$.tw.
39. or/26-38
40. and/25,39
41. limit 40 to yr="1990 - 2006"
42. limit 41 to english language
43. animal/ not (human/ or (human/ and animal/))
44. 42 not 43

The MeSH terms were amended as appropriate when the search was run in the other databases.

These searches returned the following results:

Table 1: Search results 1990-2006

Database	**Results**
Medline	1488
Embase	1596
CCTR	95
CDSR & DARE	29
Cinahl	196
Amed	8
Total	**3412**
Total after de-duplication	**2376**

Of these 2376 references, 60 were selected for review, however, due to the quality and relevance of the literature, the search was re-run from 1980-1989, using the same combination of text words and MeSH terms.

The following results were returned:

Table 2: Search results 1980-1989

Database	**Results**
Medline	747
Embase	770
CCTR	48
CDSR & DARE	0
Cinahl	2
Amed	3
Total	1570
Total after de-duplication	1246

57 papers were retrieved as a result of this search, but for the same reasons as before, the search was again extended. The search was re-run on Medline from 1966-79 and on Psycinfo from 1966-2006 (it had not been previously searched). The same search terms as before were used, however the MeSH terms VITAMIN D DEFICIENCY/, OSTEOMALACIA/ and RICKETS/ were also included, as there were reputedly higher incidences of these diseases. This search returned 883 unique results, 30 of which were retrieved.

Searches were also conducted to find grey literature relevant to the guidance. The following databases were searched: DH-Data and the King's Fund. The text word vitamin d was used as the search term in both cases. From these databases, 81 unique records were returned, and nine retrieved.

In addition to these systematic searches, the websites of the NHS Health Technology Assessment Programmes, SIGN, National Guideline Clearing House, NICE, and TRIP were searched using “vitamin d” AND “pregnancy” and “vitamin d” AND “children” as keywords, however there were no relevant results.

A search was also carried on the incidence of osteomalacia and rickets in children, restricted to the year between 1990 to 2006. There were 61 papers identified and seven were retrieved.

We also retrieved 44 papers from references list of included studies and background papers. The total number of papers retrieved for examination was 207, of which 21 papers reporting on 16 studies were eligible for review.

Table 3: Summary of search results

Source/Search	**Unique Results**	**Papers Retrieved**
Vitamin D 1990-2006	2376	60
Vitamin D 1980-1989	1246	57
Vitamin D 1966-1979	883	30
Vitamin D Grey Literature	81	9
Incidence of osteomalacia & Rickets 1990-2006	61	7
Reference Lists & Background Papers		44
Total	**4647**	**207**

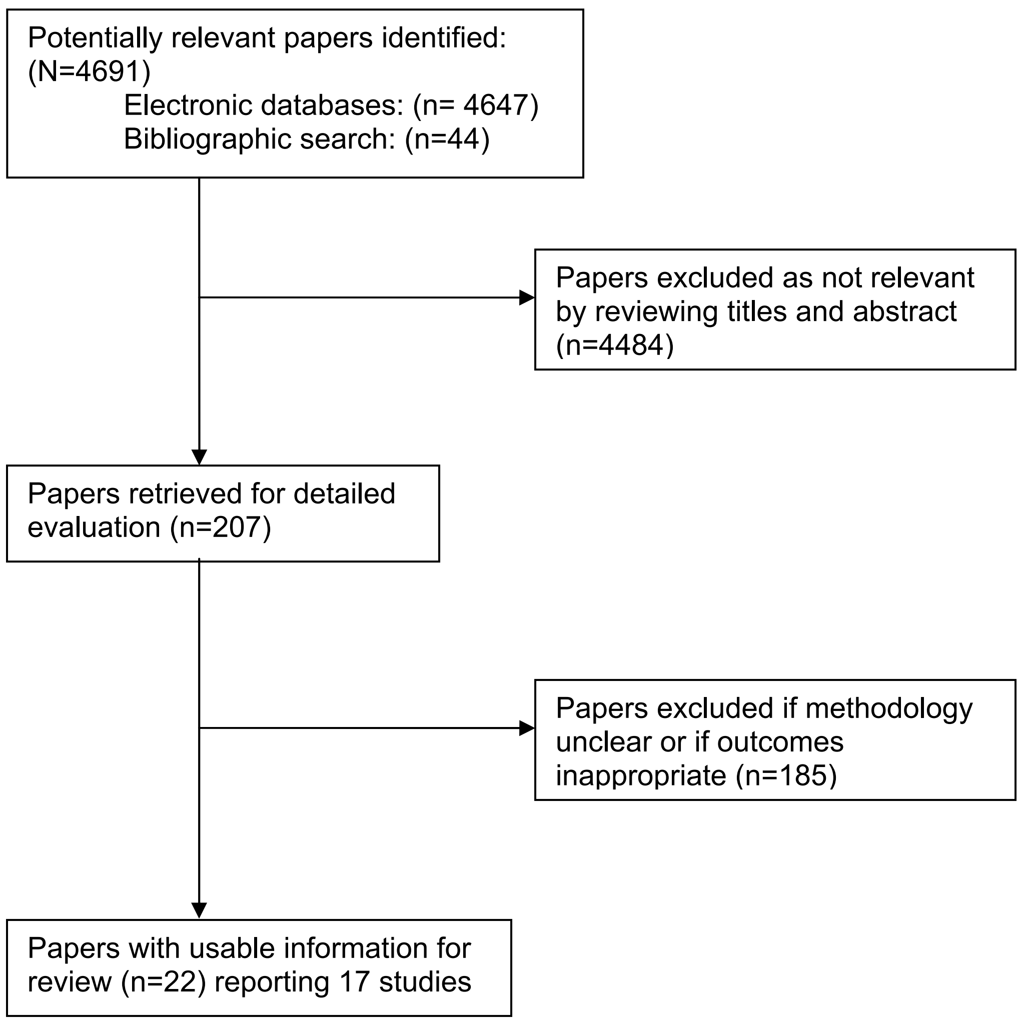
7.2 Appendix 2

Type and quality of evidence for studies on the efficacy of interventions
Adapted from the Scottish Intercollegiate Guidelines Network (2001).

Type and quality of evidence	
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs (including cluster RCTs) with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs (including cluster RCTs) with a low risk of bias
1–	Meta-analyses, systematic reviews of RCTs, or RCTs (including cluster RCTs) with a high risk of bias
2++	High quality systematic reviews of these types of studies, or individual, non-RCTs, case-control studies, cohort studies, CBA studies, ITS, and correlation studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well conducted non-RCTs, case-control studies, cohort studies, CBA studies, ITS and correlation studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2–	Non-RCTs, case-control studies, cohort studies, CBA studies, ITS and correlation studies with a high risk – or chance – of confounding bias, and a significant risk that the relationship is not causal
3	Non-analytic studies (for example, case reports, case series)
4	Expert opinion, formal consensus
NB: for policy interventions, then CBA can be awarded level 1 evidence.	

7.3 Appendix 3

Figure 1 Summary of search results



7.4 Appendix 4: List of included studies

	Stand alone vitamin D supplementation
	UK studies
1	Brooke OG, Brown IR, Bone CD *et al.* Vitamin D supplements in pregnant Asian women: effects on calcium status and fetal growth. *British Medical Journal* 1980; 280:(6216)751-4. Maxwell JD, Ang L, Brooke OG, Brown IR. Vitamin D supplements enhance weight gain and nutritional status in pregnant Asians. *Br J Obstet Gynaecol* 1981; 88(10):987-91. Brooke OG, Butters F, and Wood C. Intrauterine vitamin D nutrition and postnatal growth in Asian infants. *British Medical Journal* 1981; 283:1024.
2	Stephens WP, Klimiuk PS, Berry JL *et al*. Annual high-dose vitamin D prophylaxis in Asian immigrants. *Lancet* 1981; 2 :(8257)1199-202.
3	Cockburn F, Belton NR, and Purvis RJ. Maternal vitamin D intake and mineral metabolism in mothers and their newborn infants. *British Medical Journal* 1980; 281:(6232)11-4.
4	Pietrek J, Preece MA, Windo J *et al.* Prevention of vitamin-D deficiency in Asians. *Lancet* 1976; 1:(7970)1145-8.
5	Congdon P, Horsman A, and Kirby PA. Mineral content of the forearms of babies born to Asian and white mothers. *British Medical Journal* 1983; 286:(6373)1233-5.
6	Datta S, Alfaham M, Davies DP *et al.* Vitamin D deficiency in pregnant women from a non-European ethnic minority population--an interventional study. *BJOG: an International Journal of Obstetrics and Gynaecology* 2002; 109:(8)905-8.
	European studies
7	Mallet E, Gugi B, Brunelle P *et al.* Vitamin D supplementation in pregnancy: a controlled trial of two methods. *Obstetrics and Gynecology* 1986; 68:(3)300-4.
8	Delvin EE, Salle BL, Glorieux FH *et al.* Vitamin D supplementation during pregnancy: effect on neonatal calcium homeostasis. *The Journal of pediatrics* 1986; 109:(2)328-34.
9	la-Houhala M. 25-Hydroxyvitamin D levels during breast-feeding with or without maternal or infantile supplementation of vitamin D. *Journal of Pediatric Gastroenterology and Nutrition* 1985; 4:(2)220-6.
	US studies
10	Hollis BW and Wagner CL. Vitamin D requirements during lactation: high-dose maternal supplementation as therapy to prevent hypovitaminosis D for both the mother and the nursing infant. *American Journal of Clinical Nutrition* 2004; 80:(6 Suppl)1752S-8S.
11	Greer FR and Marshall S. Bone mineral content, serum vitamin D metabolite concentrations, and ultraviolet B light exposure in infants fed human milk with and without vitamin D2 supplements. *The Journal of pediatrics* 1989; 114:(2)204-12.
12	Greer FR, Searcy JE, and Levin RS. Bone mineral content and serum 25-hydroxyvitamin D concentration in breast-fed infants with and without supplemental vitamin D. *Journal of Pediatrics* 1981; 98:(5)696-701. Greer FR, Searcy JE, Levin RS *et al.* Bone mineral content and serum 25-hydroxyvitamin D concentrations in breast-fed infants with and without supplemental vitamin D: one-year

	follow-up. *Journal of Pediatrics* 1982; 100:(6)919-22.
	Vitamin D Health education programmes
13	Henderson JB. A health education campaign to prevent osteomalacia in Asian women in Glasgow; 1984-86. *Journal of Human Nutrition and Dietetics* 1989; 2:(4)237-49.
14	Dunnigan MG, Glekin BM, Henderson JB *et al.* Prevention of rickets in Asian children: assessment of the Glasgow campaign. *British Medical Journal Clinical Research Ed.* 1985; 291:(6490)239-42. Dunnigan MG, McIntosh WB, Sutherland GR *et al.* Policy for prevention of Asian rickets in Britain: a preliminary assessment of the Glasgow rickets campaign. *British Medical Journal Clinical Research Ed.* 1981; 282:(6261)357-60.
15	Save the Children Fund. Stop rickets campaign; report of a health education campaign published by the Save the Children Fund on behalf of the DHSS Asian Working Group. London: Save the Children Fund on behalf of the DHSS Asian Working Group; 1983.
16	Stephens WP, Klimiuk PS, Warrington S *et al.* Observations on the natural history of vitamin D deficiency amongst Asian immigrants. *Quarterly Journal of Medicine* 1982; 51:(202)171-88. Stephens WP, Klimiuk PS, Warrington S. Preventing vitamin D deficiency in immigrants: is encouragement enough? *Lancet*. 1981; 25;1(8226):945-6.
17	Box V. Rickets; what should the health education message be? *Health Visitor* 1983; 56:(4)131-4.

7.5 Appendix 5: List of excluded studies

1.	Bibliographic Information	Reason for rejecting study
1	Brech DM. Vitamin and mineral diet adequacy and supplement use by full-time employed women with preschool children. *Journal of the American Dietetic Association* 1999; 99:(10)1267-9.	Non-intervention study
2.	British Nutrition Foundation. A critical review of the psychosocial basis of food choice and identification of tools to effect positive food choice: a summary. No. NO9017. 2004.	Policy paper
3.	Brooke OG. Supplementary vitamin D in infancy and childhood. *Archives of Disease in Childhood* 1983; 58:(8)573-4.	Discussion paper
4.	Brooke OG, Brown IR, and Cleeve HJ. Vitamin D deficiency in Asian immigrants. *British Medical Journal* 1979; 2:(6183)206.	Non-intervention study
5.	Brooke OG. Vitamin D metabolism in preterm infants. *Lancet* 1983; 2:(8355)913.	Preterm infants
6.	Brooks MH, Stern PH, and Bell NH. Vitamin D-dependent rickets type II. *New England Journal of Medicine* 1980; 302:(14)810.	Non intervention study
7.	Brunvand L and Lindemann R. [How to achieve an optimal intake of vitamin D in children].[see comment]. [Norwegian]. *Tidsskrift for Den Norske Laegeforening* 2000; 120:(6)735.	Paper in Norwegian
8.	Brunvand L, Henriksen C, and Haug E. [Vitamin D deficiency among pregnant women from Pakistan. How best to prevent it?]. [Norwegian]. *Tidsskrift for Den Norske Laegeforening* 1996; 116:(13)1585-7.	Paper in Norwegian
9.	Callaghan AL, Moy RJBIW, Debelle GD *et al.* Incidence of symptomatic vitamin D deficiency. *Archives of Disease in Childhood* . 2006.	Non-intervention study
10.	Callaghan AL, Booth IW, Moy RJ *et al.* Rickets returns. *Archives of Disease in Childhood* 2002; 86:(Supp 1)A35.	Non-interventional study
11.	Cancer Research UK. SunSmart: Stay safe. http://www.cancerresearchuk.org/sunsmart/staysafe/children/ [online] 2006	For reference only
12.	Cesur Y, Caksen H, Gundem A *et al.* Comparison of low and high dose of vitamin D treatment in nutritional vitamin D deficiency rickets. *Journal of Pediatric Endocrinology* 2003; 16:(8)1105-9.	Study in developing country
13.	Cooke R, Hollis B, Conner C *et al.* Vitamin D and mineral metabolism in the very low birth weight infant receiving 400 IU of vitamin D. *Journal of Pediatrics* 1990; 116:(3)423-8.	Low birth weight infants
14.	Crocombe S, Mughal MZ, and Berry JL. Symptomatic vitamin D deficiency among non-Caucasian adolescents living in the United Kingdom. *Archives of Disease in Childhood* 2004; 89:(2)197-9.	Non-interventional study

1.	Bibliographic Information	Reason for rejecting study
15.	Dandona P. Osteomalacia presenting as pathological fractures during pregnancy in Asian women of high social class. *British Medical Journal Clinical Research Ed.* 1985; 290:(6481)1591.	Non intervention study
16.	Das G, Crocombe S, McGrath M *et al.* Hypovitaminosis D among healthy adolescent girls attending an inner city school. *Archives Disease in Childhood* . 2005.	Non-interventional study
17.	Davies PS, Bates CJ, Cole TJ *et al.* Vitamin D: seasonal and regional differences in preschool children in Great Britain.[erratum appears in Eur J Clin Nutr 1999 Jul;53(7):584]. *European Journal of Clinical Nutrition* 1999; 53:(3)195-8.	Non intervention study
18.	Dawson KP and Mondhe MS. Nutritional rickets among the immigrant population of Bradford. *Practitioner* 1972; 208:(248)789-91.	Non intervention study
19.	de Torrente de la Jara, Pecoud A, and Favrat B. Female asylum seekers with musculoskeletal pain: the importance of diagnosis and treatment of hypovitaminosis D. *BMC Family Practice* 2006; 7:4.	A non-RCT in Europe
20.	Dent CE and Gupta MM. Plasma 25-hydroxyvitamin-D-levels during pregnancy in Caucasians and in vegetarian and non-vegetarian Asians. *Lancet* 1975; 2:(7944)1057-60.	Non intervention study
21.	Department of Health. Delivering Healthy Start. A guide for health professionals in Devon and Cornwall. 2005.	For reference only
22.	Department of Health. Hospital Episode Statistics. Department of Health [online] 2006 Available from: URL:http://www.hesonline.nhs.uk	For reference only
23.	Docio S, Riancho JA, Perez A *et al.* Seasonal deficiency of vitamin D in children: a potential target for osteoporosis-preventing strategies? *Journal of Bone and Mineral Research* 1998; 13:(4)544-8.	Not in scope
24.	Dunnigan MG. Asian rickets and osteomalacia in Britain. *Child nutrition and its relation to mental and physical development* , 43-70. 1977. Kellogg Company of Great Britain. Manchester.	Insufficient usable data
25.	Dunnigan MG and Ford JA. Prevention of rickets and osteomalacia in Asians. *Lancet* 1977; 2:(8034)412-3.	Discussion paper
26.	Ebeling PR. Megadose therapy for vitamin D deficiency. *Medical Journal of Australia* 2005; 183:(1)4-5.	Non-intervention study
27.	Ellis G, Woodhead JS, and Cooke WT. Serum-25-hydroxyvitamin-D concentrations in adolescent boys. *Lancet* 1977; 1:(8016)825-8.	Non intervention study
28.	Evans JR, Allen AC, Stinson DA *et al.* Effect of high-dose vitamin D supplementation on radiographically detectable bone disease of very low birth weight infants. *The Journal of pediatrics* 1989; 115:(5 Pt 1)779-86.	Low birth weight infants
29.	Felton DJ and Stone WD. Osteomalacia in asian immigrants during pregnancy. *British Medical Journal* 1966; 5502:1521-2.	Inappropriate outcome
30.	Finch PJ, Ang L, Eastwood JB *et al.* Clinical and histological spectrum of osteomalacia among Asians in south London. *Quarterly Journal of Medicine* 1992; 83:(302)439-48.	Non intervention study
31.	Ford JA. Asian rickets and osteomalacia. *Nursing Times* 1974; 70:(2)49-50.	Discussion paper

1.	Bibliographic Information	Reason for rejecting study
32.	Ford JA, McIntosh WV, Butterfield R *et al.* Clinical and subclinical vitamin D deficiency in Bradford children. *Archives of Disease in Childhood* 1976; 51:(12)939-43.	Non intervention study
33.	Ford JA, Davidson DC, McIntosh WB *et al.* Neonatal rickets in Asian immigrant population. *British Medical Journal* 1973; 3:(5873)211-2.	Case study of one patient
34.	Ford JA. Rickets and osteomalacia: high risk for Asian immigrants in Britain. *Nursing Mirror* 1979; 149:(18)36-7.	Discussion paper
35.	Gardee R and Greaves D. Infant-feeding practices among immigrants in Glasgow. *British Medical Journal* 1978; 2:(6150)1498.	Non intervention study
36.	Gartner LM, Greer FR, Section on Breastfeeding and Committee on Nutrition *et al.* Prevention of rickets and vitamin D deficiency: new guidelines for vitamin D intake. *Pediatrics* 2003; 111:(4 Pt 1)908-10.	Non-intervention study
37.	Gillies DRN, Hay A, Sheltawy MJ *et al.* Effect of phototherapy on plasma 25(OH)-vitamin D in neonates. *Biology of the Neonate* 1984; 45:(5)225-7.	Not in scope
38.	Glerup H, Rytter L, Mortensen L *et al.* Vitamin D deficiency among immigrant children in Denmark. *European Journal of Pediatrics* 2004; 163:(4-5)272-3.	Non-intervention study
39.	Goel KM, Sweet EM, Logan RW *et al.* Florid and subclinical rickets among immigrant children in Glasgow. *Lancet* 1976; 1:(7970)1141-5.	Non intervention study
40.	Goel KM. Proceedings: Rickets in Asian children in Glasgow. *Scottish Medical Journal* 1975; 20:(4)188.	Non intervention study
41.	Goel KM, Campbell S, and Sweet EM. Reduced prevalence of rickets in Asian children in Glasgow. *Lancet* 1981; 2:(8243)405-6.	Non intervention study
42.	Greer FR, Steichen JJ, and Tsang RC. Effects of increased calcium, phosphorus, and vitamin D intake on bone mineralization in very low-birth-weight infants fed formulas with Polycose and medium-chain triglycerides. *Journal of Pediatrics* 1982; 100:(6)951-5.	Low birth weight infants
43.	Grindulis H, Scott PH, Belton NR *et al.* Combined deficiency of iron and vitamin D in Asian toddlers. *Archives of Disease in Childhood* 1986; 61:(9)843-8.	Not in scope
44.	Gupta MM, Round JM, and Stamp TC. Spontaneous cure of vitamin-D deficiency in Asians during summer in Britain. *Lancet* 1974; 1:(7858)586-8.	Non intervention study
45.	Haddad JG. Vitamin D--solar rays, the Milky Way, or both? *New England Journal of Medicine* 1992; 326:(18)1213-5.	Non-intervention study
46.	Haider SA. Letter: Screening for rickets. *British Medical Journal* 1974; 3:(5932)688-9.	Not in scope
47.	Hamaoui E and Hamaoui M. Nutritional assessment and support during pregnancy. *Gastroenterology Clinics of North America* 1998; 1998 Mar;27:(1)89-121.	Discussion paper
48.	Harbour R and Miller J. A new system for grading recommendations in evidence based guidelines. *British Medical Journal* 2001; 323:(7308)334-6.	Methodological reference

1.	Bibliographic Information	Reason for rejecting study
49.	Harris RJ, Armstrong D, Ali R *et al.* Nutritional survey of Bangladeshi children aged under 5 years in the London borough of Tower Hamlets. *Archives of Disease in Childhood* 1983; 58:(6)428-32.	Non intervention study
50.	Harrison S, Buttner P, and Nowak M. Maternal beliefs about the reputed therapeutic uses of sun exposure in infancy and the postpartum period. *Australian Midwifery* 2005; 18:(2)22-8.	Not in scope
51.	Harrison SL, Buettner PG, and MacLennan R. Why do mothers still sun their infants? *Journal of Paediatrics and Child Health* 1999; 35:(3)296-9.	Not in scope
52.	Hartman JJ. Vitamin D deficiency rickets in children: prevalence and need for community education. *Orthopaedic Nursing* 2000; 19:(1)63-7.	Discussion paper
53.	Heckmatt JZ, Peacock M, Davies AE *et al.* Plasma 25-hydroxyvitamin D in pregnant Asian women and their babies. *Lancet* 1979; 2:(8142)546-8.	Non intervention study
54.	Henriksen C, Brunvand L, Stoltenberg C *et al.* Diet and vitamin D status among pregnant Pakistani women in Oslo. *European Journal of Clinical Nutrition* 1995; 49:(3)211-8.	Non-intervention study
55.	Herrera AJ, Salcedo UT, and Ruiz MP. Vitamin D supplementation and rickets in very low birth weight infants. *Pediatric Research* 1981; 15:(4 II)1323.	Low birth weight infants
56.	Hillman LS, Hollis B, Salmons S *et al.* Absorption, dosage, and effect on mineral homeostasis of 25-hydroxycholecalciferol in premature infants: comparison with 400 and 800 IU vitamin D2 supplementation. *Journal of Pediatrics* 1985; 106:(6)981-9.	Premature infants
57.	Hillman LS, Salmons S, and Dokoh S. Serum 1,25-dihydroxyvitamin D concentrations in premature infants: preliminary results. *Calcified Tissue International* 1985; 37:(3)223-7.	Premature infants
58.	Hodgkin P, Hine PM, Kay GH *et al.* Vitamin-D deficiency in Asians at home and in Britain. *Lancet* 1973; 2:(7822)167-71.	Non intervention study
59.	Holick MF. High prevalence of vitamin D inadequacy and implications for health.[see comment]. [264 refs]. *Mayo Clinic Proceedings* 2006; 81:(3)353-73.	Non-intervention study
60.	Holick MF. Sunlight "D"ilemma: risk of skin cancer or bone disease and muscle weakness. *Lancet* 2001; 357:(9249)4-6.	Not in scope
61.	Hollingworth J, Hawley JH, Davidson AC *et al.* Severe vitamin D deficiency in pregnancy. *Journal of Obstetrics and Gynaecology* 1994; 14:(6)430-1.	Non intervention study
62.	Holmes AM Enoch BA, Taylor JL, and Jones ME. Occult rickets and osteomalacia amongst the Asian immigrant population. *Quarterly Journal of Medicine* 1973; 42:(165)125-49.	Non intervention study
63.	Howarth AT. Biochemical indices of osteomalacia in pregnant Asian immigrants in Britain. *Journal of Clinical Pathology* 1976; 29:(11)981-3.	Non intervention study
64.	Iqbal SJ, Kaddam I, Wassif W *et al.* Continuing clinically severe vitamin D deficiency in Asians in the UK (Leicester). *Postgraduate Medical Journal* 1994; 70:(828)708-14.	Non-interventional study
65.	Javaid MK, Crozier SR, Harvey NC *et al.* Maternal vitamin D status during pregnancy and childhood bone mass at age 9	Non-interventional study

1.	Bibliographic Information	Reason for rejecting study
	years: a longitudinal study. *Lancet* 2006; 367:(9504)36-43.	
66.	Katbamna S. The needs of asian carers. A selective literature review. No. WP50 11/96 SK/PB. University of Leicester, Nuffield Community Care Studies Unit; 1997.	No information on vitamin D
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7	Deqiong MA and Jones G. The association between bone mineral density, metacarpal morphometry, and upper limb fractures in children: a population based case control study. The Journal of Endocrinology and Metabolism 2003; 88 (4): 1486-91.	Case control study on bone mass and bone fractures.
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