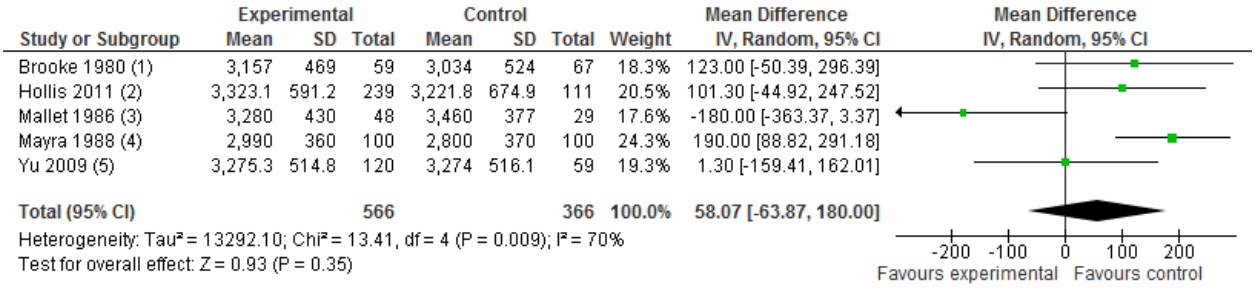
Supplementary material: Vitamin D during pregnancy and maternal, neonatal and infant health outcomes: a systematic review and meta-analysis

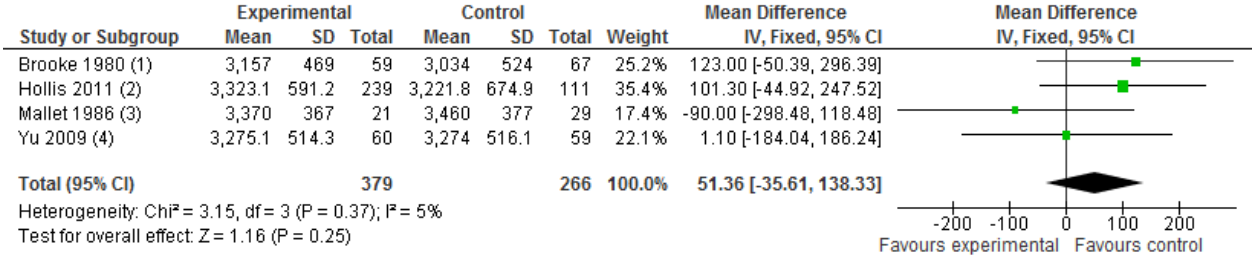
Figure S1. Trials and observational studies of vitamin D supplementation and mean birthweight (in grams)

Combined bolus or daily dosing and mean birthweight



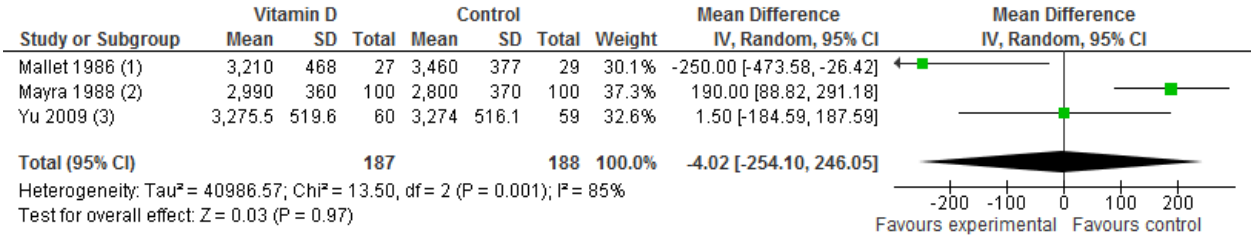
(1) Intervention 1000 IU D2 daily vs. placebo control
(2) Intervention group pooled 2000 IU D3/day and 4000 IU D3/day groups; comparison with 400 IU D3/day
(3) Intervention group pools daily dose 1000 IU D2 and single 200,000 IU at month 7. Presented variance assumed to be SE.
(4) Intervention: 2 doses 600,000 IU D3, one each in month 7 and 8 in pregnancy vs no supplementation
(5) Intervention group pooled 800 IU/daily with bolus 200,000 IU group vs no supplementation

Trials with daily dosing only



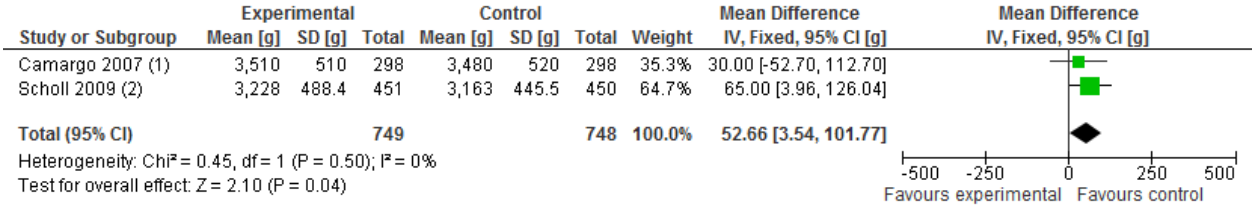
(1) Intervention 1000 IU D2 daily vs. placebo control
(2) Intervention group pooled 2000 IU D3/day and 4000 IU D3/day; comparison with 400 IU D3/day.
(3) Intervention group daily 1000 IU D2 vs no supplementation. Presented variance assumed to be SE.
(4) Intervention group 800 IU/daily vs. no supplementation

Trials using large bolus dose only



(1) Bolus dose 200,000 IU D2 at month 7 vs. no supplementation. Presented variance assumed to be SE.
(2) 2 doses 600,000 IU D3, one each in month 7 and 8 in pregnancy vs. no supplementation
(3) Bolus dose 200,000 IU at month 7 vs. no supplementation

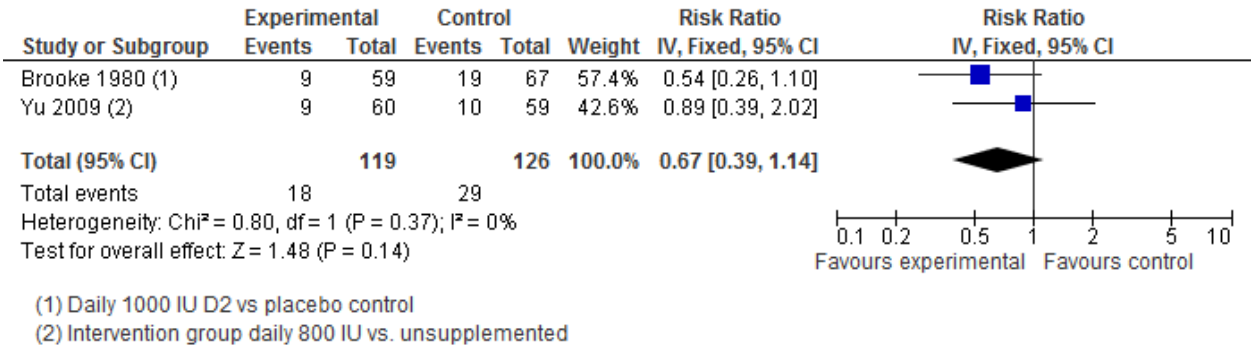
Observational studies of intake



(1) "Experimental" >658 IU; Comparison <446 IU/day
(2) "Experimental": >535 IU/day; Comparison <185 IU/day

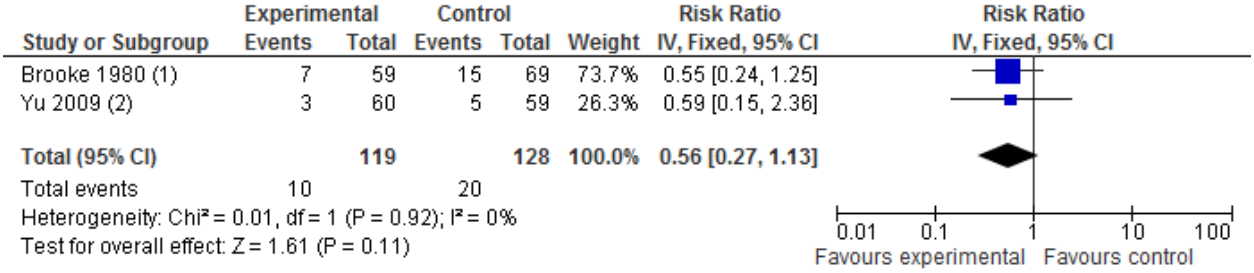
Figure S2. Trials of vitamin D supplementation and SGA and low birthweight, disaggregated by dosing approach

Daily supplementation and small-for-gestational age



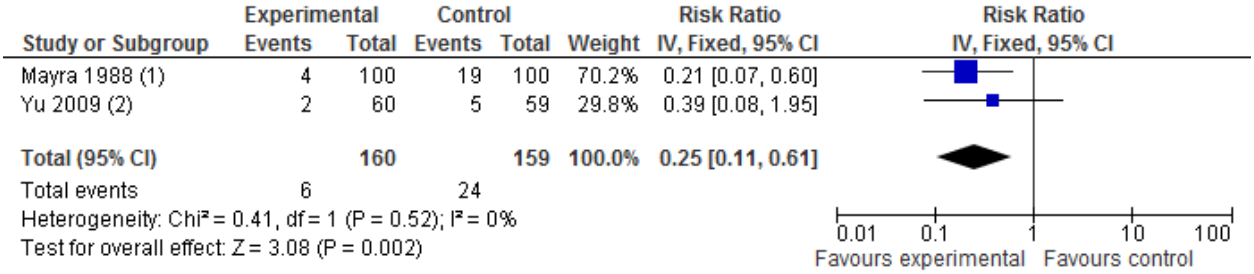
(1) Daily 1000 IU D2 vs placebo control
(2) Intervention group daily 800 IU vs. unsupplemented

Daily supplementation and low birthweight



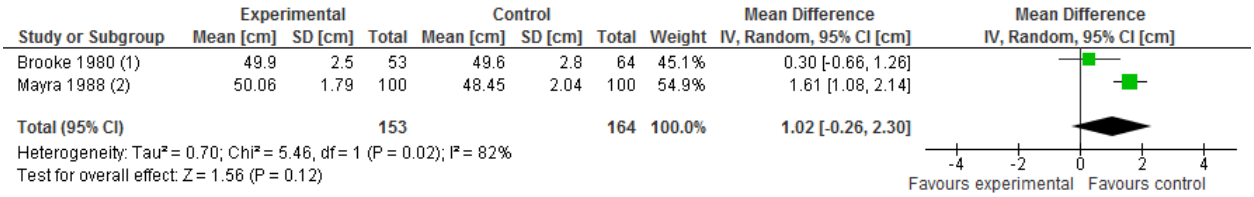
(1) Intervention 1000 IU D2 daily vs. placebo control
(2) Intervention group 800 IU/daily vs. no supplementation

High dose bolus supplementation and low birthweight



(1) Intervention group received 600,000 IU vitamin D3 at 7th and 8th month of gestation
(2) Intervention group received bolus 200,000 IU vs. no supplementation

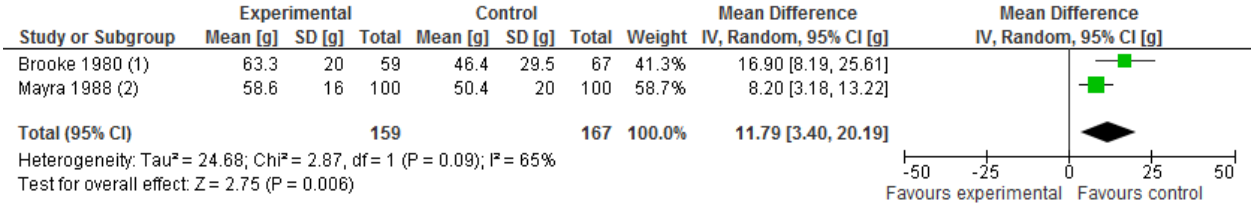
Figure S3. Trials of vitamin D supplementation and mean crown-heel length (in cm.)



(1) Intervention 1000 IU D2 daily vs. placebo control

(2) Intervention: 2 doses 600,000 IU vitamin D3, once each in month 7 and 8 in pregnancy vs. no supplementation

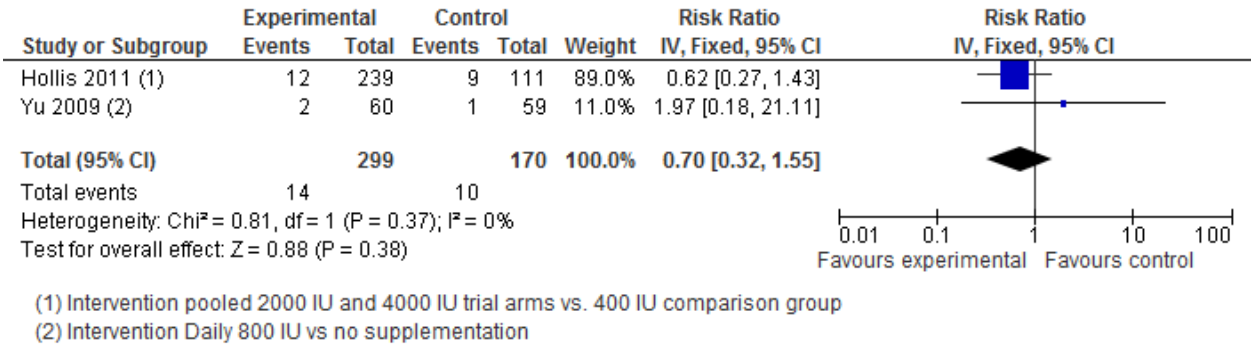
Figure S4. Trials of vitamin D supplementation and mean daily weight gain during the 3rd trimester (in grams)



(1) Intervention 1000 IU D2 vs. placebo control
(2) Intervention: 2 doses 600,000 IU D3, one each in month 7 and 8 in pregnancy vs. no supplementation

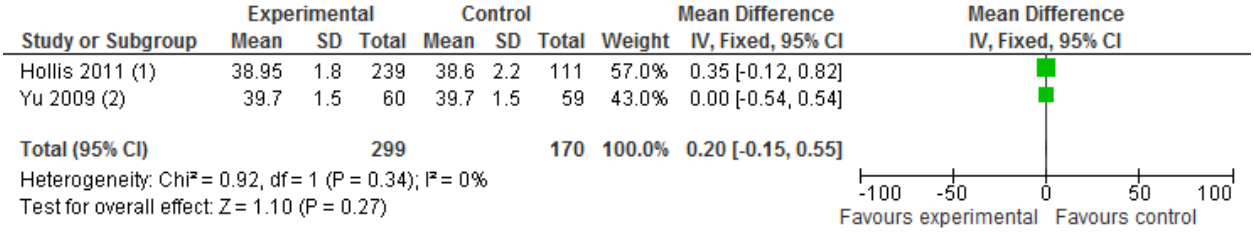
Figure S5. Supplementation and preterm delivery and mean duration of gestation, disaggregated by dosing approach

Daily supplementation and preterm delivery (<37 weeks)



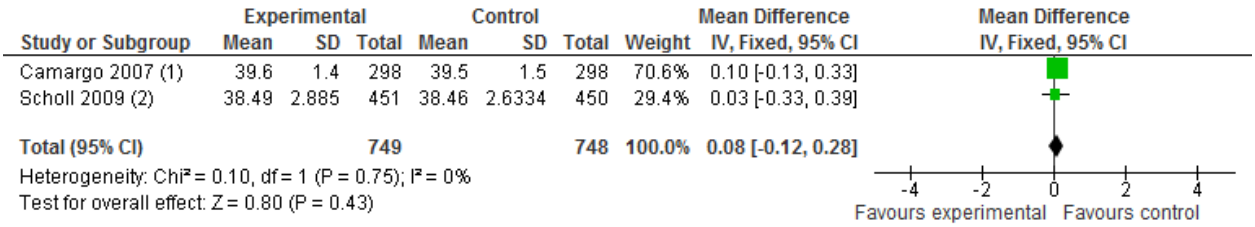
(1) Intervention pooled 2000 IU and 4000 IU trial arms vs. 400 IU comparison group
(2) Intervention Daily 800 IU vs no supplementation

Daily supplementation and mean gestational age at delivery



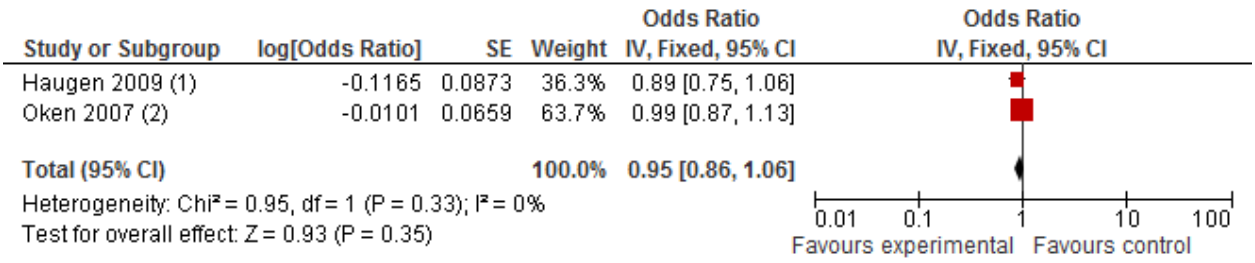
(1) Intervention 4000 IU D3 vs. 400 IU comparison
(2) Intervention group daily 800 IU D2 vs no supplementation

Figure S6. Observational studies of vitamin D intake and mean gestational age



(1) Top vs. bottom quartile of vitamin D intake during pregnancy, Bottom <446 IU, Top >659
(2) Top vs. bottom quintile of intake, Bottom <284 IU, Top >535 IU

Figure S7. Observational studies of vitamin D intake and pre-eclampsia risk



(1) Comparison is of total vitamin D intake <200 IU vs. >800 IU assessed by FFQ for the first 4-5 months of pregnancy
(2) OR is for each 100 IU increase in intake during the first trimester

Table S1. Search strategy and keywords

For the search we included #1 AND #2 AND #3-7. The search was restricted to human studies.

#	Search	Details
1	Vitamin D	"Vitamin D"[Mesh] OR vitamin D*[Text Word] OR "25-hydroxyvitamin D"[Substance] OR "25-hydroxyvitamin D"[Text Word])
2	Pregnancy	"Pregnancy"[Mesh] OR PREGNANT[Text Word] OR PREGNANCY[Text Word] OR ANTEPARTUM[Text Word] OR PRENATAL[Text Word] OR ANTE-PARTUM[Text Word] OR PRE-NATAL[Text Word] OR PREPART*[Text Word] OR ANTENATAL[Text Word]
3	Low birthweight due to IUGR	"Fetal Growth Retardation"[Mesh] OR "Fetal Growth Retardation"[Text Word] OR "Pregnancy Outcome"[Mesh] OR "Pregnancy outcome"[Text Word] OR "Birth Weight"[Mesh] OR "Birth weight"[Text Word] OR "birthweight"[Text Word] OR "Infant, Low Birth Weight"[Mesh] OR "Body Size"[Mesh] OR "Fetal Development"[Mesh] OR fetal development OR "Growth"[Mesh] OR growth[Text Word] OR "Fetal Diseases"[Mesh] OR "fetal diseases"[Text Word] OR "Growth Disorders"[Mesh] OR growth disorders[Text Word] OR "Infant, Small for Gestational Age"[Mesh] OR "small for gestational age"[Text Word] OR "Fetal Diseases/prevention and control"[Mesh] OR "crown-heel"[Text Word] OR "length"[Text Word] OR "intra-uterine growth retardation"[Text Word] OR "IUGR"[Text Word]
4	Preterm birth	"Premature Birth"[Mesh] OR premature birth OR "Obstetric Labor, Premature"[Mesh] OR "Infant, Premature"[Mesh] OR prematurity[Text Word] OR premature[Text Word] OR "gestational length"[Text Word]
5	Neonatal and child growth**	"Growth"[Mesh] OR "Growth Disorders"[Mesh] OR "Nutritional Status"[Mesh] OR stunt*[Text Word] OR underweight[Text Word] OR wast*[Text Word] OR "Body Height"[Mesh] OR "Body Weight"[Mesh] OR "height"[Text Word] OR "weight"[Text Word] OR "Anthropometry"[Mesh] OR Anthropom*[Text Word]
6	Neonatal and child mortality and morbidity	"Infant Mortality"[Mesh] OR "Perinatal Mortality"[Mesh] OR "Child Mortality"[Mesh] OR "mortality"[Text Word] OR "neonatal mortality"[Text Word] OR "hemorrhage"[Text Word] OR "Hemorrhage"[Mesh] OR "Asphyxia"[Mesh] OR "Asphyxia Neonatorum"[Mesh] OR "asphyxia" OR "Sepsis"[Mesh] OR "sepsis"[Text Word] OR "morbidity"[Text Word] OR "infection"[Text Word] OR "Respiratory Tract Infections/blood"[Mesh] OR "Respiratory Tract Infections"[Mesh] OR "acute lower respiratory infection"[Text Word] OR "ALRI"[Text Word] OR "ARI"[Text Word] OR "acute respiratory infection"[Text Word] OR "Diarrhea"[Mesh] OR "diarrhea"[Text Word] OR "Measles"[Mesh] OR "measles"[Text Word] OR "Infectious Disease Transmission, Vertical"[Mesh] OR "Malaria"[Mesh] OR "malaria" OR "HIV"[Mesh] OR "HIV" OR "Disease Progression"[Mesh] OR "Disease Transmission, Infectious"[Mesh] OR "HIV Infections"[Mesh] OR "vertical transmission"[Text Word] OR "mother-to-child transmission"[Text Word]
7	Maternal morbidity and mortality from hemorrhage, sepsis and obstructed labor	"Maternal Mortality"[Mesh] OR "Maternal mortality"[Text Word] OR "Pregnancy Complications"[Mesh] OR "pregnancy complications"[Text Word] OR "Obstetric Labor Complications"[Mesh] OR "obstructed labor"[Text Word] OR "Sepsis"[Mesh] OR "sepsis"[Text Word] OR "Hemorrhage"[Mesh] OR "hemorrhage"[Text Word] OR obstructed labo*

OR "Pregnancy Outcome"[Mesh])

We searched the Cochrane central register of controlled trials searched using ("vitamin D"[Mesh] or "vitamin D" or "25-hydroxyvitamin D") AND ("Pregnancy"[Mesh] OR PREGNANT OR PREGNANCY OR ANTEPARTUM OR PRENATAL OR ANTE-PARTUM OR PRE-NATAL OR PREPART* OR ANTENATAL) in Clinical Trials

Table S2. Evaluation of the quality of eligible trials for potential inclusion in the meta-analysis

Author, year (ref.)	Trial design	Adequate sequence generation?	Adequate allocation concealment?	Blinding	Loss to follow-up	Intention to treat analysis?	Free of selective reporting?	Other bias (e.g., small sample size)?	Comments	Grade
Brooke (1980)[52, 69, 91]	RCT	Unclear	Unclear	Double blind (but no mention of packaging)	3.7% withdrew from the study, 3% excluded based on criteria	Yes	Unclear	Relatively small sample size, no power calculations		Moderate (small sample size)
Hollis (2011)[5]	RCT	Unclear (described as stratified block randomization)	Unclear (allocation based on baseline 25(OH)D levels; unclear blinding of investigators or participants)	Double Blind	129/479 women exited before delivery due to low adherence/ poor attendence	Yes	Unclear	Purposive allocation of women with 25(OH)D levels >150 nmol/L may have led to bias though most baseline characteristics were comparable (gravidity, parity, insurance differed marginally across groups). Exited women differed by a number of characteristics.	Adjustment by race may correct for some bias	Moderate (high loss to follow-up, randomization, small sample size)
Mallet (1986)[51]	RCT	Yes (random number table)	Unclear	No (no placebo was used), but measurements and data collection were blinded	None (not mentioned)	Yes (Not mentioned explicitly)	Unclear	Small sample size	Unclear whether randomization was used to allocate controls or just treatment groups.	Moderate (No placebo control)
Mayra (1981)[43]	Non randomized study	No	No	No	Unclear (Did not appear prospectively	Unclear	Unclear	Small sample size in control group, potential for bias if study not	Daily vitamin D group also received calcium; unclear whether high dose group also	Very low (Strong potential for bias from non-randomized

					designed)			prospective	received calcium	design, lack of clarity on whether it was a prospective study)
Mayra (1988)[46]	Rando mized	Unclear	Unclear	No (no placebo)	Unclear (100 in final analysis but unclear how many dropouts/e xclusions)	Unclear	Unclear	Method of randomization unclear; 100 women per group in final analysis after an unknown number of exclusions; baseline characteristics comparable by group		Low (unclear randomization method, no placebo control, unclear dropout/exclusi ons)
Yu (2009)[42]	RCT	Yes (computer generated random lists, blocks of 15 within each ethnic group)	No (Study personnel not blinded to treatment assignment)	No (no placebo)	<1% loss to follow-up; 6% excluded for various reasons	Yes	Unclear			Moderate (no placebo control, small study)

Table S3. Evaluation of the quality of evidence of individual observational studies for potential inclusion in the meta-analysis[1]

Author, year (ref.)	Study design	Concurrent controls, if appropriate?	Adjustment for confounding, if appropriate?	Attrition	Other bias?	Other study strengths?	Comments	Grade
Mannion, 2006[45]	Prospective Cohort	Yes	Yes	3.7%	Not adjusted for energy intake, calcium or other nutrients, race, or UV exposure. Potential selection bias due to purposive inclusion of 'milk restrictors'	Moderate n, Two 24-hour recalls	Downgraded due to potential for confounding and selection bias.	Very Low
Camargo, 2007[60]	Prospective Cohort	Yes	No	Unclear	No adjustment for confounding on birth outcomes	Large sample size		Low
Oken, 2007[89]	Prospective Cohort	Yes	Yes	Unclear, 81% had sufficient information for analysis.	Good adjustment for confounding			Moderate
Baker, 2009[66]	Prospective cohort	Yes	Unclear (specific details not provided for vit. D analysis)	Maximum of 4.4% (for SGA)		Large n, multiethnic population	Few details about analysis given; unclear which analyses were pursued or which confounders used in models.	Moderate
Scholl, 2009[63]	Prospective cohort	Yes	Yes	Unclear	Did not adjust for UV exposure or season	Large n, multiethnic population, adjusted for energy,	Observational study upgraded due to large sample size, adjustment for many confounders, examination by quintiles	Moderate

						ethnicity, other factors, examined by quintile	of intake rather than just dichotomous	
Erkkola, 2009[44]	Prospective cohort	Yes	No	0.2%	Unadjusted analysis, documented associations between vitamin D intake and potential confounders	Large n, validated FFQ	Observational study downgraded due to lack of multivariate analysis and potential for confounding	Very Low
Haugen, 2009[74]	Prospective Cohort	Yes	Yes	Dropout unclear; 78% had data on food intake, 74% had data on sup use.	Good adjustment for confounding;	Very large n	Confounding: Did not include energy intake in models but did adjust for BMI, exposure categorized in 200 IU increments of intake.	Moderate (upgraded due to large sample size, strong analysis)
Watson 2010[53]	Prospective Cohort	Yes	Yes	Unclear: data presented from 87% of recruited subjects	Adjusted birthweight for gestational age, maternal weight, but not energy, SES or UV exposure		Only presented p-values in tables; effect estimate for interquartile effect of vitamin D presented in text but unclear whether it was adjusted or which measure it corresponded to.	Low

Table S4. Prospective observational studies of the relationship between maternal blood levels of 25(OH)D during pregnancy and measures of fetal growth, birth weight, and preterm birth

Author (yr)	Population and study design	Assay timing and method	Categories and adjustment for confounding	Findings
Morley et al (2006)[30, 58]	Geelong, Australia. Largely Caucasian population (n=374)	25(OH)D measured twice, once at median 11 wks and again at 28-32 weeks using RIA (IDS)	25(OH)D<28nmol/L adjusted for infant sex, maternal height, whether first child, smoking in pregnancy and season of blood sample	Compared with ≥28nmol/L measured at 28-32 weeks, infants of vitamin D deficient women did not significantly differ in birth weight (-153g; 95% CI -348,42), crown-heel length (-0.6cm (-1.5,0.3), gestation length (-0.8 wks; -1.4, 0.2) .
Clifton-Bligh et al (2008)[59]	Austalian population, 55% of European descent, mean age 32 y attending metropolitan obstetric clinic (n=307), 6% took supplement with 500 IU D_3	25(OH)D measured at mean 28.7 weeks(nearly all from 2nd or 3rd trimester) using Nichols Advantage Assay	Unclear analysis of the relationship between 25(OH)D and birthweight related measures; appeared to be examined as a continuous variable, unclear whether univariate or multivariate.	Maternal 25(OH)D not associated with infant birthweight, length or head circumference after adjusting for gestational age (P>0.4 for all).
Gale et al (2008)[54, 70]	Southhampton UK (n=466), median serum 25(OH)D: 50 nmol/L.	25(OH)D measured at week 34 using RIA (IDS)	Categories of 25(OH)D: <30, 30-50, 51-75, >75. Did not appear to adjust for confounders	Mean birthweight calculated by linear regression did not differ (p=0.247), not did length (p=0.150).
Baker (2009)[62]	London and Manchester UK (n=306)	25(OH)D measured at week 30 using straight phase HPLC	Methods section suggested univariate and multivariate models though actual methods used for this analysis was unclear.	"Serum 25(OH)D did not differ significantly by pregnancy outcome"; no data reported or specific reference to which outcomes were examined although paper included preterm delivery (<37 weeks), SGA<10th and <5th percentile, and a number of other outcomes.
Bowyer (2009)[56]	Sydney, Australia. Cohort study of 971 women prior to 28 weeks gestation, 55% born in Austalia. 40 vitamin D deficient women were treated	25(OH)D assessed at 30-32 weeks gestation and at delivery using Nichols Advantage assay.	25(OH)D treated as a categorical exposure using cutoff of ≤ 25 nmol/L for deficiency and 26-50nmol/L as insufficiency. Multivariate models include gestation, maternal age and overweas maternal birth place. Mode of delivery included normal vaginal,	Offspring of mothers with vitamin D deficiency had significantly lower birth weight unadjusted difference 198g (95% CI 90,305), adjusted difference 151g (50, 250). No difference between cord 25(OH)D and birth weight. Mode of delivery not significantly associated with maternal vitamin D levels.

	with supplements.		assisted vaginal or C-section.	
Farrant (2009)[9]	Mysore, India (n=559) singleton pregnancies, non diabetic, <32 weeks gestation. Supplementation with calcium and 250 IU vitamin D_3 common, mean 66% had 25(OH)D<50nmol/L, 31%<28nmol/L.	Serum 25(OH)D measured at 30±2 weeks gestation using RIA (IDS)	Dichotomous cutoff of <50nmol/L used to define deficiency; Analyses adjusted for maternal age, fat mass, and diabetes	No relationships found between maternal vitamin D status and mean birthweight (p=0.8) or crown-heel length (p=0.9). Comparison presented means for deficient vs. all subjects presented.
Mehta et al (2009)[48, 49]	Tanzania, HIV+ women (n=884)	25(OH)D measured 12-25 weeks, mean ≈week 20 using RIA (Nicholas)	Continuous and dichotomous 25(OH)D (cutoff 80nmol/L) used; adjusted for multivitamin supplementation, maternal age, CD4 counts, HIV disease stage at baseline	In multivariate adjusted models, no significant differences in low birthweight RR=0.84 (0.55-1.28), preterm birth (RR=0.84 (0.65-1.07)), early preterm birth <34 weeks (RR=0.77 (0.50-1.18), SGA 1.25 (0.82-1.90), Composite adverse pregnancy outcome indicator: RR: 0.92 (0.76-1.12).
Prentice (2009)[47]	The Gambia (rural): 25-OH-D levels at 20 weeks pregnancy ranged from 50-150 nmol/L (n=125)	25(OH)D Samples taken at 20 and 36 weeks using RIA (Diasorin)	Plasma 25(OH)D examined as continuous at weeks 20, 36, and average of both, and dichotomous using <80 nmol/L cutpoint, adjusted for season, maternal height, weight, weight gain, supplement group, sex of infant.	No significant relationship between maternal vitamin D status and birth weight, infant weight, length or other measures .
Bodnar (2010)[62]	Pittsburgh, USA: Nested case-control study, singleton pregnancies with blood sample <22 weeks. 77 white, 34 black with SGA births vs. 196 white and 105 black non-SGA births	25(OH)D collected <22 weeks, median 9-10 weeks, assessed using ELISA from IDS, validated against HPLC.	Cubic splines used to explore continuous relationships and quartiles and cutoffs including <37.5nmol/L, 37.5-75nmol/L, >75 nmol/L. Models adjusted for prepregnancy BMI, smoking, SES, maternal age, gest. Age at blood sample, marital status, insurance status, smoking prior to pregnancy, periconceptional multivitamin use, preconception	Among black women, no relationships between vitamin D status and risk of SGA observed. In white women, U-shaped curve was observed with least risk between 60-80 nmol/L. Using 37.5-75nmol/L as comparison group, OR for SGA were as follows: <37.5: 7.5 (1.8-31.9): >75nmol/L: 2.1 (1.2, 3.8).

			physical activity.	
Leffelaar (2010)[57]	Amsterdam, The Netherlands, multi-ethnic population, singleton at-term births (n=3730)	25(OH)D measured at mean of 13-14 weeks using OCTEIA immunoenzymometric assay (IDS)	Cutoffs of 25(OH)D used to compare deficient (<30 nmol/l), insufficient (30-49.9 nmol/l), and adequate (>50 nmol/l). Multivariate adjusted for infant sex, maternal height, parity, maternal age, smoking, pre-preg. BMI, education, ethnic group, vitamin D (presumably season of collection).	Multivariate adjusted SGA (Adequate reference): deficient OR 1.9 [95% CI 1.4, 2.7], insufficient OR 1.2 [0.9, 1.3]. Birthweight: deficient -68.3 [-107.5, -29.0], insufficient -1.8 [-37.6, 34.0]. Unadjusted SGA at birth (%): def: 14.8, Insuff. 9.4, Adequate: 6.8, p<0.001. Significant effects observed on mean birthweight (def: 3418g, insuff. 3505g, sufficient 3559g), p<0.001,
Shand (2010)[90]	Vancouver, Canada. 221 singleton pregnancies, mostly white and Asian ethnicity. Women recruited from 10 to ≈20 weeks with either clinical or biochemical risk factors for pre-eclampsia. More than 95% used supplements. Median 25(OH)D levels were 47.7 nmol/L	25(OH)D measured between 10 and 20 weeks gestation (mean 18.7 weeks) using RIA (Diasorin)	25(OH)D examined as a continuous variable and categorized using cutoffs of <37.5, <50, <75 nmol/L vs. ≥75nmol/L (ref). Adjusted for maternal age, ethnicity, parity, BMI, season, multivitamin use and smoking status.	When using 25(OH)D as a continuous variable no statistically significant effect on adverse pregnancy outcomes including preterm birth, birthweight <3rd centil, fetal death. Results not included in review for these outcomes because the population was pre-selected as being at-risk of pre-eclampsia.
Viljakainen (2010)[55]	Caucasian nonsmoking primaparous mothers with singleton pregnancies in Finland (n=125), excluded 1 IUGR infant	25(OH)D levels measured at week 8-10 of gestation and at 2 days postpartum using OCTEIA immunoenzymometric assay (IDS)	Mean value of two 25(OH)D measures was used to define status and cutoff 42.6nmol/liter for dichotomous comparisons. 25(OH)D during first trimester examined as continuous variable. Multivariate adjusted for parental size, maternal weight gain during pregnancy, solar exposure, total vitamin D intake, initial 25OHD.	"In multivariate analysis…higher birth weight Z-score but not birth length was associated only weakly with decreased maternal 25(OH)D, p=0.07," (presumably using cord blood levels). Below vs. above median 25(OH)D ± sd: Unadjusted mean birth weight: 3700 ± 400g vs. 3520g ± 440g, P=0.052)

				Unadjusted z score birth weight: 0.12 ± 0.81 vs. -0.23 ± 1.09, p=0.082. Unadjusted mean birth length: 51.0 ± 1.9cm vs.50.5 ± 1.8cm, P=0.140. Unadjusted z score birth length: 0.14 ± 1.0 vs. -0.20 ± 0.96, p=0.104.
Shibada (2011)[64]	Japan. 93 pregnant women >30 weeks gestation attending hospital for routine pregnancy checkup.	25(OH)D measured after week 30 in pregnancy with with RIA (Diasorin).	Comparison of mean 25(OH)D levels by outcome. Multivariate linear regression with age, albumin, BAP, Serum NTx, Serum corrected Ca, Serum Pi.	Serum levels of women with threatened premature delivery (28.0 ± 8.0 nmol/L) significantly ($p<0.05$) lower than others (38.0 + 12.8nmol/L). In multiple regression greater 25(OH)D levels found to be significant independent predictors of risk of preterm delivery (p=0.023).

Table S5. Prospective observational studies of the relationship between maternal blood levels of 25(OH)D during pregnancy and pre-eclampsia

Author (yr)	Population and study design	Assay timing and method	Categories and adjustment for confounding	Findings
Bodnar (2007)[65]	Pittsburgh, USA. Nested case control study of nulliparous women who developed pre-eclampsia (n=55) and who did not develop pre-eclampsia (n=219).	25(OH)D assessed prior to 22 weeks gestation (median 10.4 weeks) using ELISA from IDS.	25(OH)D treated as a continuous exposure as well as using thresholds of <37.5nmol/L, 37.5-75nmol/L and >75 nmol/L. Analysis adjusted for race/ethnicity, season, gestational age of sample, pre-pregnancy BMI and education.	25(OH)D <37.5 nmol/L increased odds of preeclampsia (AOR 5.0 [95% CI 1.7, 14.1]). Monotonic dose response relationship observed with each 50nmol/L decline in 25(OH)D associated with increased odds of preeclampsia risk: AOR 2.4 [1.1, 5.4).
Powe (2010)[67]	Massachusetts, USA. Nested case control of cases with pre-eclampsia (n=39) and normotensive controls (n=131).	First trimester blood samples; mean gestational age at blood collection 11.5 weeks, mass spectroscopy used to assess 25(OH)D.	25(OH)D treated as a continuous variable, by quartiles, and as a categorical variable deficiency (<37.5nmol/L). Adjusted for BMI, nonwhite race, and summer blood collection.	For each 25nmol/L increase in 25(OH)D, AOR for PE: 1.24 (95% CI 0.78, 1.98); for dichotomous cutoff <37.5nmol/L AOR 1.35 (95% CI 0.40, 4.50).
Baker (2010)[66]	North Carolina, USA. Nested case control study of cases who developed severe pre-eclampsia (n=51) vs. race matched controls with uncomplicated pregnancies (n=204)	25(OH)D assessed in mid pregnancy at mean 17 weeks using mass spectroscopy	Analysed using lowess plot to examine continuous risk as well as by cutoffs of <50, 50-74.9, and >75 nmol/L. Multivariate analysis adjusted for season of blood draw, maternal age, multiparity, BMI, and gestational age at serum collection.	Serum 25(OH)D<50nmol significantly increased risk of severe pre-eclampsia AOR: 5.51 (2.02-14.52), p=0.001 compared with $\geq$75nmol. Trend toward significance for women with levels 50-74.9 nmol/L AOR: 2.16 (0.86, 5.40), p=0.10.
Shand (2010)[68]	Vancouver, Canada. Prospective study of 221 singleton high risk pregnancies, mostly white and Asian ethnicity with very high supplement use. Median 25(OH)D levels were 47.7 nmol/L, 12.7% developed pre-eclampsia	Serum 25(OH)D measured between 10 and 20 weeks gestation (mean 18.7 weeks) using Diasorin RIA	Categorized using cutoffs of <37.5, <50, <75 nmol/L and as continuous variable	When using 25(OH)D as a continuous variable no statistically significant effect. In adjusted analysis no significant differences in risk of pre-eclampsia or gestational hypertension. AOR for <37.5 nmol/L: 0.91 [0.31, 2.62]; <50 nmol/L: 1.39 [0.54, 3.53], <75 nmol/L: 0.57 (0.19, 1.66] compared with >75nmol/L.

Table S6. Baseline and attained levels of maternal 25(OH)D at delivery in trials

Trial	Baseline 25(OH)D	Achieved maternal 25(OH)D at delivery
Brooke (1980)[52, 69, 91]	At 28 weeks Mean 25(OH)D: Control: 20.0 nmol/L Daily: 20.2 nmol/L	Control: 16.2 ± 2.7 nmol/L Daily: 168.0 ± 12.5 nmol/L
Hollis (2011)[5,b]	Mean baseline 25(OH)D by group: 400 IU/day: 61.6 ± 27.1 nmol/L 2000 IU/day: 58.3 ± 22.3 nmol/L 4000 IU/day: 58.2 ± 21.8 nmol/L	400 IU/day: 78.9 ± 36.5 nmol/L 2000 IU/day: 98.3 ± 34.2 nmol/L 4000 IU/day: 111.0 ± 40.4 nmol/L
Mallet (1986)[51]	Only levels 25(OH)D at delivery were presented	Mean ± SD Control: 9.4 ± 4.9 nmol/L Daily: 25.3 ± 7.7 nmol/L Bolus: 26.0 ± 6.4 nmol/L
Mayra (1988)[46]	25(OH)D levels not assessed.	25(OH)D levels not assessed.
Yu (2009)[42]	At 27 weeks, median (IQR) 25(OH)D by group: (1) Control: 25 nmol/L (21-38) (2) Daily: 26 nmol/L (30-37) (2) Bolus dose: 26 nmol/L (21-44)	Follow-up at delivery (1) Control: 27 nmol/L (27-39) (2) Daily: 42 nmol/L (31-76) (2) Bolus dose: 34 nmol/L (30-46) At delivery 40% had 25(OH)D levels <25 nmol/L in the group receiving no supplementation vs. 13% and 7% in the daily and bolus dose groups respectively.