Evidence table 1.Characteristics of the studies evaluating calcium and bone health outcomes

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| --- | --- | --- | --- | --- | --- | --- |
| Author  Year  Study type | Study design | Population, N  Gender  Age | Intervention  Duration  Calcium source | Outcomes | Results | Score |
| Chung et al. 2009 (18) | SLR | Ottawa report +4 RCTs | Calcium supplement+vitamin D | BMC, hip, lumbar spine and total body BMD | Small increase in BMC, and in BMD in different sites, reduction in fractures in institutionalized people, 2000 mg calcium plus 20 µg vitamin D reduce the stress fracture risk in 17 to 35 year old women | A |
| Huncharek et al. 2008 (7) | Meta-analysis | 21 trials  n=3,821  <18 years | Calcium/milk supplement  12 to 48 months | Total body BMC (12 trials)  lumbar spine BMC (4 trials) | No effect: mean difference (95% CI): Total body BMC 2.05 g (-3.26 to7.36) in calcium treated subjects | C |
| Papaioannou et al.  2009 (20) | SLR | Men  >50 y  14 studies out of 25 included calcium intake  N ranging from 137 to 5,995  5 longitudinal  9 cross-sectional studies | Food or supplements | Lumbar spine, proximal femur BMD | Inconsistent evidence for both cross-sectional and longitudinal studies. | C |
| Shea et a.  2002 (17) | SLR | 15 trials BMD as an outcome  N= 1,806, out of them 953 calcium supplemented  5 trial fractures as an outcome  N=576 women  >45 y | 500 – 2,000 mg/d,  vitamin D allowed if ≤400 IU/d  >12 mo | Change in BMD (lumbar spine, hip, distal radius)  vertebral (5) and non- vertebral (2) fractures | Reduced bone loss in calcium treated, mean difference (95% CI):  Spine: 1.66% (0.92 to 2.39),  Hip:1.64% (0.70 to 2.57)  Distal radius:1.91% (0.33 to 3.50)  No effect on fractures:  Vertebral fractures RR (95% CI): 0.77 (0.54; 1.09)  Non-vert fractures RR: 0.86 (0.43; 1.72) | C |
| Bischoff-Ferrari et al. 2007 (22) | Meta-analysis | 7 of 8 prospective cohort studies included 170 991 women and 2954 hip fractures  5 studies included 68 606 men and 214 hip fractures  5 of 7 trials included 5,666 women and 1,074 men with 814 nonvertebral fractures  4 of 5 RCTs included 6504 subjects with 139 hip fractures | 800-1000 mg/d in trials | Hip fractures and non-vertebral fractures | No effect: RR (95% CI) in cohort studies high versus low calcium intake  hip fractures: for women 1.01 (0.97; 1.02) and for men 0.92 (0.82; 1.03)  in RCTs  non-vertebral (5 RCTs): 0.92 ( 0.81; 1.05)  hip fractures (4 RCTs): 1.64 (1.02; 2.64) | C |
| Tang et al.  2007 (21) | Meta-analysis | 29 trials:  12 fracture and BMD  5 fracture only  12 BMD only  ≥50 years | 500-1,500 mg/d  in 13 trials vitamin D 200-800IU/d | Fractures of any type  BMD | For calcium only RR for fracture reduction: 0.90 (0.80; 1.00) ; calcium without or with vitamin D: RR 0.88, 95% CI 0.83-0.95; p=0.0004treatment effect was greater when calcium intake was < 700 mg/d  reduced bone loss in Ca and CaD treated  Hip: 0.54% (0.35 to 0.73)  spine: 1.19% (0.76 to 1.61) | A |
| Vatanparast et al.  2010 (5) | Cohort | N=152 (85 boys and 67 girls)  9-18-years | Food and supplements if used | Total body BMC | Boys accrued more TBBMC during their peak years (aged 14-16) than girls during their peak years (ages 12-14)  Net accrual in boys through adolescence was 31% greater than in girls. The peak accrual Ca per unit height was achieved at the age of peak height velocity in both sexes.  Boys and girls aged 9-13 would require 1000-1100 mg/d, and from age 14 to 18, requirements would be 1000 mg/d for girls and 1200 mg/d for boys | C |
| Warensjö et al.  2011 (23) | Cohort | N=61 433 women for fratures  N=5022 for osteoporosis | Total calcium intake | Fractures of any type and hip fractures  Osteoporosis | HR (95% CI) for any fracture: 1.18 (1.12 to 1.25) and for hip fractures: 1.29 (1.17 to 1.43) higher in the lowest quintile compare with the third quintile (reference group)  OR for osteoporosis 1.47 (1.09 to 2.00)  The highest vs. the third quintile the rate of any fracture and the rate of osteorosis were similar, whereas the hip fx rate was raised (HR: 1.19; 1.06 to 1.32) | C |
| Waugh et al.  2009 (16) | SLR | 4 studies out of 13 evaluated calcium  N=3653 women  40-60 years | current Ca intake (4)  past (1) | BMD | Inconsistent evidence.  In one study OR (95% CI) 0.85 (0.74 to 0.97) in trochanter BMD  Low milk intake during early adulthood was associated with lower spinal BMD | C |
| Winzenberg et al.  2006/2010 (6) | SLR | 19 trials  N=2859 (Ca: 1367 vs. Pl: 1426)  3-18 years | Calcium supplementation including food supplementation vs. placebo  ≥ 3 months | Total body BMC  BMD of the femoral neck, spine and upper limb | Mean difference (95% CI)  Total body BMC: 0.14 g (0.01 to 0.27)  No significant effect in femoral neck or spine BMD.Distal radius BMD: 0.14 (0.04 to 0.24)  1.7% greater radial BMD increase in supplemented groups  Only the effect in the upper limb persisted after supplementation cease (0.14; 0.01 to 0.28). | A |
| Yin et al.  2010 (9) | Cohort | Birth cohort of 216 boys and girls  at the age of 16 years | Maternal diet  16 years follow up | BMD at the femoral neck, lumbar spine and total body | Positive association between calcium intake and lumbar spine BMD (p<0.05) | C |
| Zhong et al.  2009 (24) | Cross-sectional | 2006 out of 2371  ≥50 y postmenopausal women | Total calcium intake in three categories:  <400 mg; 400-1200 mg; >1200 mg/d | Fractures | No association between calcium intake and risk of fracture | C |

Evidence table 2. Characteristics of the studies evaluating calcium and pregnancy related health outcomes

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| --- | --- | --- | --- | --- | --- | --- |
| Author  Year  Study type | Study design | Population, N  Gender  Age | Intervention  Duration  Calcium source | Outcomes | Results | Score |
| Abalos et al.  2010 (8) | RCT | N=510 (Ca 259, Placebo 251)  pregnant women | 1500 mg vs. placebo  20 -36 weeks gestation, delivery  Ca-supplements | Fetal somatic or skeletal growth  ultrasound examinations | No differences between groups at each of the gestational ages  Neonatal characteristics and anthropometric measurements at delivery were comparable in both groups | C |
| Bergel and Barros  2007 (26) | SLR | 2 RCT and 3 observational studies  Offsprings of healthy primiparous women  age <12 months, N=1310  age from 1 to 9 years, N=935 | Maternal calcium intake during pregnancy  in 2 RCTs 2000 mg/d as Ca supplements  in observational studies Food or use of Ca-supplements | Offspring diastolic and systolic blood pressure in mmHg | Higher maternal Ca intake was associated with a reduction (95% CI) of 1.92 mmHg (0.71 to 3.14) in systolic blood pressure of 1 to 9-year old offspring  Inconsistent results among infants | B |
| Buppasiri et al.  2011 (25) | SLR | 21 RCTs  N=16,602 pregnant women | Calcium supplements | Maternal, fetal and neonatal outcomes (not hypertension) | Mean difference ( 95% CI) in birth weight of 64.66 g (15.75 to 113.58) favouring Ca-supplemented groups  No difference in other outcomes | A |
| Hofmeyr et al.  2010 (27) | SLR | 15 RCTs N=15,730 pregnant women | Calcium intake at least 1g daily vs. placebo during pregnancy | High blood pressure  Pre-eclampsia | Reduction in the average risk with calcium supplementation compared to placebo:  High blood pressure RR= 0.65 (95% CI 0.53 to 0.81).  Pre-eclampsia RR=0.45 (0.31 to 0.65)  Preterm birth RR 0.76 (0.60 to 0.97) | A |
| Yin et al.  2010 (9) | Cohort | Birth cohort of 216 boys and girls  at age of 16 years | Maternal diet  16 years follow up | BMD at the femoral neck, lumbar spine and total body | Positive association between maternal calcium intake and lumbar spine BMD (<0.05) of the offspring | C |

Evidence table 3. Characteristics of the studies evaluating calcium and cancer

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| --- | --- | --- | --- | --- | --- | --- |
| Author  Year  Study type | Study design | Population, N  Gender  Age | Intervention  Duration  Calcium source | Outcomes | Results | Score |
| Carroll et al.  2010 (31) | SLR | 6 RCTs  N=19 151 men and women  16-79-y | Calcium supplementation 1000-2000 mg/d  6 months to 7 years | Recurrence of adenomas and occurrence of colorectal cancer | 20% lower risk for adenoma recurrence  RR = 0.80 (95% CI; 0.69 to 0.94) for those on calcium from 1200 to 2000 mg/d  No effect in advanced adenoma; RR=0.77 (0.50 to 1.17)  Calcium with or without vitamin D had no effect on the RR for colorectal cancer, RR=0.62 (0.11 to 3.40) in general population | C |
| Chen et al.  2010 (28) | Meta-analysis | 15 studies: 6 cohorts and 9 case-control studies  females | Food or supplemental calcium | Breast cancer | 19% decrease in breast cancer risk for those in the highest quintile of calcium intake compared to those with lowest Ca-intake  RR=0.81 (0.72 to 0.90) | C |
| Chung et al.  2009 (18) | SLR | Male and female  all age groups | Vitamin D and calcium together or alone | Cancers | HR (95% CI) for total cancer 0.89 (0.77 to 1.03)  In cohort studies Ca-intake ranging from 750 to 1750 mg/d in premenopausal women was associated with a decreased risk of breast cancer, but no association in postmenopausal women  For prostate cancer three of four cohort studies found significant association between higher Ca intake (>1500 mg or > 2000 mg) and increased risk of prostate cancer, compared to men consuming lower amount of Ca (500-1000 mg/d) | A |
| Hjartåker et al.  2010 (29) | Cohort | 64,904 women with 1,407 diagnosed breast cancer  born between 1927-1965 | Dairy consumption and calcium intake  1996/1999 through 2006 | Breast cancer | Calcium intake was not significantly related with breast cancer: HR (95% CI)  0.65 (0.39 to 1.08) for premenopausal  0.85 (0.70 to 1.04) for postmenopausal women | B |
| Kristal et al.  2010 (33) | Cohort | N=9,559 men  > 55 yrs | 7 years  Nutrient intake from food and supplements including calcium | Prostate cancer | Dietary calcium intake was positively associated with low-grade cancer (quartile 4 vs. quartile 1)  OR (95% CI) =1.27 (1.02 to 1.57)  Inverse association with high-grade cancer, OR= 0.43 (0.21 to 0.89) | B |
| Ma and Chapman  2009 (32) | SLR | Articles from 1996 to 2008, included if level of evidence IIIb or greater  men | Food and supplements | Prostate cancer | Inconclusive results regarding dairy products or calcium. 2 meta-analyses suggested slightly increased risk, while 3 from 5 large cohort studies found no association, one found negative and one positive association | C |
| Mahabir et al.  2010 (35) | Cohort | 482,875 participants  288,257 men and 194,618 women  with 7,052 lung cancer  50-71 at baseline | 7 years (1995-2003)  Total intake (food and supplements) of several minerals, including Ca (other ones: Mg, Fe, Zn, Cu, Se) | Lung cancer | No association between total calcium intake and lung cancer risk in all subjects.  Higher calcium intake quintiles of current smokers had decreased relative risk of lung cancer (p for trend =0.02). | B |
| McCullough et al.  2008 (34) | SLR | 5 case-control studies  N=6,163 women  1,410 cases and 4,753 controls  18 to 81 years | Food and supplements | Endometrial cancer | No significant association between calcium intake and endometrial cancer, OR (95% CI)  OR=0.92 (0.68 to 1.25) | C |
| Weingarten et al.  2008 (30) | SLR | 2 RCTs  N=1346 men and women with previous adenomas  35-80-y | Calcium carbonate 1200 mg  or calcium gluconate 2000 mg/d vs. placebo  1-4 (mean of 4 and 3 years) | Colorectal cancer and adenomatous polyps | Reduced OR (95% CI) for the development of recurrent colorectal adenoma OR= 0.74, (0.58 to 0.95) | A |

Evidence table 4. Characteristics of the studies evaluating calcium and cardiovascular outcomes

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| --- | --- | --- | --- | --- | --- | --- |
| Author  Year  Study type | Study design | Population, N  Gender  Age | Intervention  Duration  Calcium source | Outcomes | Results | Score |
| Bergel and Barros  2007 (26) | SLR | 2 RCT and 3 observational studies  Offsprings of healthy primiparous women  age <12 months, N=1310  age from 1 to 9 years, N=935 | Maternal calcium intake during pregnancy  in 2 RCTs 2000 mg/d as Ca supplements  in observational studies Food or use of Ca-supplements | Offspring diastolic and systolic blood pressure in mmHg | Higher maternal Ca intake was associated with a reduction (95% CI) of 1.92 mmHg (0.71 to 3.14) in systolic blood pressure of 1 to 9-year old offspring  Inconsistent results among infants | B |
| Bhakta et al.  2009 (36) | Cohort | N= 257, (144 women ) out of  514 at baseline  > 60 years | 4-y follow-up  use of supplements | Aortic valve calcification (AVC)  Coronary artery calcification (CAC)  Blood pressure  Serum lipids (total chol, HDL, LDL, triglyc), GFR | Calcium supplementation did not affect the progression of AVC or CAC.  No significant difference in renal function, diabetes, hypertension, cholesterol or BMI | C |
| Bolland et al.  2010 (43) | Meta-analysis | 15 RCTs: 11 double blinded,  5 with patients level data, N=8151)  and 11 with trial level data (N=11,921)  men and women 51-77 years | Ca-supp >500 mg/d  > one year (2 to 4 years) | Myocardial infarction, stroke or death | HR (95%CI) between Ca-supplemented and placebo groups  Myocardial infarction: 1.31 (1.02 to 1.67) Analysis of trial level data showed increased incidence of myocardial infarction in those allocated to calcium (pooled relative risk 1.27, 95% confidence interval 1.01 to 1.59, P=0.038)  No significant results for stroke or death. | C |
| Chung et al.  2009 (18) | SLR | Male and female  all age groups | Vitamin D and calcium together or alone | CVD, blood pressure | Ca-supplementation (400-2000 mg/d) lowered systolic blood pressure significantly in hypertensives by2-4 mmHg, but not diastolic blood pressure | A |
| Dickinson et al. 2006 (45) | SLR | 13 RCTs  N= 485  adults ≥18-y with primary hypertension (>140/85 mmHg) | Calcium as supplements, or dietary intervention trying to manipulate only Ca-intake  8-15 weeks | SBP and DBP | Mean (95% CI) decline in supplemented compared to controls was -2.5 mmHg (-4.5 to -0.6) in SBP  No difference in DBP (-0.8; -2.2 to 0.4) | A |
| Hofmeyr et al.  2010 (27) | SLR | 15 RCTs  N=15,730 pregnant women | Calcium intake at least 1g daily vs. placebo during pregnancy | High blood pressure  Pre-eclampsia | Significant reductions in the average risk with calcium supplementation compared to placebo:  High blood pressure RR= 0.65 (95% CI 0.53 to 0.81).  Pre-eclampsia RR=0.45 (0.31 to 0.65)  Preterm birth RR 0.76 (0.60 to 0.97) | A |
| Kaluza et al.  2010 (39) | Cohort | N=23,366  men  45-79 years | 9-10 years  CVD and cancer 1998 to 2006  All cause mortality to 2007  Dietary calcium intake, supplements users excluded | Cardiovascular disease | Calcium intake was not significantly associated with lower CVD mortality HR 0.77 (95% CI 0.58 to 1.01) | B |
| Lewis et al.  2011 (40) | RCT | N=1460 (730 calcium; 730 placebo)  >70-years women | 5 years intervention  1200 mg calcium carbonate/d (2 \* 600 mg) or placebo  4.5 years follow-up | Atherosclerosis vascular disease (ACVD) | No significant results for total population.  In 5-y analysis Calcium supplementation was associated with a significant decrease in the risk of participants sustaining ASVD events (multivariate-adjusted HR = 0.438, 95% CI 0.246–0.781, p = .005). This effect dissipated in the 9.5-year analysis. | B |
| Reid et al.  2010 (37) | RCT | N=323 men  ≥40 y | 2 years  Ca-supplement 600 mg or 1200 mg/d, or Placebo | Total cholesterol,  HDL, LDL, triclycerides  Blood pressure  Fat and lean mass  Cardiovascular health | No significant effect on lipids or body composition  In those with dietary calcium intake below median intake Ca-supplementation (1200 mg)decreased systolic blood pressure compared to placebo placebo, −3.0 ± 1.3 mm Hg; Ca1200, −7.2 ± 1.9 mm Hg(p<0.05) | C |
| van der Pols et al.  2009 (38) | Cohort | N=4374  Men and women  65 years | 1937-39 family food consumption  1948 to 2005 cause of death  Food | Cardiovascular disease outcomes  CHD and stroke  All-cause mortality | Calcium intake was not significantly associated with stroke mortality HR 0.41 (0.16 to 1.05).  No evidence that family diet high in dairy products or milk intake was associated with CHD mortality | C |
| Wang, L, et al.  2010 (41) | SLR | 17 prospective studies or RCTs with vitamin D and/or Calcium  Out of them 4 prospective studies  4 RCTs with Ca  Men and women  Adults > 19 years | 4 prospective studies with calcium supplements at baseline  4 RCTs with calcium supplements, 400 - 1000 mg | Cardiovascular disease | Calcium supplements had no significant effect on cardiovascular events | C |
| Wang, TKM et al.  2010 (42) | RCT | N=1471 women (739 placebo; 706 calcium)  >55-yrs  323 men (placebo 107; calcium 108)  >40-yrs | 5 years women  2 y for men  1000 mg Ca for women 600 or 1200 mg Ca for men | Abdominal aortic calcification (AAC)  Coronary aortic calcification (CAC) | Neither dietary calcium nor calcium supplementation were related to changes in AAC or CAC  Vascular calcification was not related to low BMD or fractures. | C |
| Pittas et al.  2007 (44) | SLR | Men and women | Vitamin D and/or calcium supplements and dairy intake | Type 2 Diabetes (DM2) | For prospective studies OR (95% CI) for the highest vs. the lowest Ca-intake:  Incident DM2 0.82 (0.72 to 0.93)  Prevalence of metabolic syndrome 0.71 (0.57 to 0.89)  For the highest vs. lowest dairy intake:  Incident DM2 0.86 (0.79 to 0.93) | C |

Evidence table 5. Characteristics of the studies evaluating calcium and obesity/body weight outcomes

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| --- | --- | --- | --- | --- | --- | --- |
| Author  Year  Study type | Study design | Population, N  Gender  Age | Intervention  Duration  Calcium source | Outcomes | Results | Score |
| Chung et al.  2009 (18) | SLR | Male and female  all age groups  17 RCTs | Vitamin D and Ca together or alone | Growth, obesity, cancers, all mortality, CVD, blood pressure | No significant effect on body weight  No significant effect on weight and height gain in children from 3 to 18 years | A |
| Onakpoya et al  2011 (47) | SLR | 7 RCTs  N=794 mainly women | Ca-supplements vs. placebo  6-24 months  1,000-1,500 mg/d | Overweight/obesity | Mean difference (95% CI) favouring calcium  Body weight -0.74 kg (-1.00 to -0.48)  Body fat -0.93 kg (-1.16 to -0.71) | A ? |
| Reid et al.  2010 (37) | RCT | N=323 men  ≥40 y | 2 years  Ca-supplement:  600 mg or 1200 mg/d Placebo | Fat and lean mass | No effect on body composition | C |
| Trowman et al.  2006 (46) | SLR | 13 trials  4 with dairy products  8 with Ca-supplements (5 placebo-controlled)  one with tree arms used both food and supplements  24-72year mainly women | 4 trials with dairy products  9 with Ca-supplements  12 weeks to 36 months | Obesity/weight change | Neither Ca supplements nor dairy products had a significant effect on body weight. | C |
| Yanovski et al.  2009 (48) | RCT | N=340 overweight and obese adults (245 women and 95 men  18 to 80 years, mean age 38.8 | 1500 mg Calcium/placebo  2 yrs | Change in weight and body fat mass  Body composition by DXA as a secondary outcome | Nosignificant mean difference (95% CI) between Ca and placebo groups  Change in body weight 0.02 kg (-1.64 to 1.69 kg),  Body fat mass 0.39 kg (-1.04 to 1.92) | B |

Evidence table 6. Characteristics of the studies evaluating calcium and mortality

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Author  Year  Study type | Study design | Population, N  Gender  Age | Intervention  Duration  Calcium source | Outcomes | Results | Score |
| Bolland et al.  2010 (43) | SLR | 15 RCTs: 11 double blinded,  5 with patients level data, N=8151  and 11 with trial level data, N=11,921  Men and women  51-77 years | Ca-supp >500 mg/d  > one year (2 to 4 years) | Death | No significant effect on death (HR=1.09, 96% CI 0.96 to 1.23, P=0.18) | C |
| Chung et al.  2009 (18) | SLR | 1 cohort  Men and women  40-65 years | Total dietary calcium  in quintiles  lowest ≤585 mg/d  highest >1245 mg/d | All mortality | No significant effect on mortality | A |
| Kaluza, et al.  2010 (39) | Cohort | N=23,366  45-79 years  Men | 9-10 years,  CVD and cancer 1998 to 2006  All cause mortality to 2007  Dietary calcium intake, supplements users excluded | All cause mortality  Cancer mortality  Cardiovascular disease mortality | HR (95% CI) for all-cause mortality favouring high Ca-intake  0.75 (0.63 to 0.88)  No significant association for CVD mortality 0.77 (0.58 to 1.01) or  Cancer mortality 0.87 (0.65 to 1.17) | B |
| Mursu et al.  2011 (49) | Cohort | Iowa Women’s Health Study N= 38,772 older women  mean age 61.6 years at baseline 1986 | Supplements reported 1986, 1997, and 2004  mortality through 2008 (15,594 deaths) | Mortality | Inverse association between use of Ca-supplements and death, HR (95% CI) 0.91 (0.88 to 0.94)  Absolute risk reduction 3.8% | B? |
| van der Pols et al.  2009 (38) | Cohort | N=4374 men and women  65 years | 1937-39 family food consumption  1948 to 2005 cause of death | Cardiovascular disease outcomes  CHD and stroke  All-cause mortality | All-cause mortality was lowest in those with the highest family dairy use, HR (95% CI) =0.77 (0.61 to 0.98) and calcium intake, HR=0.77 (0.60 to 0.98)  No significant association with stroke mortality HR 0.41 (0.16 to 1.05).  No evidence about association with CHD mortality | C |