Original Article

The Effects of Calcium Supplementation on Verified Coronary Heart Disease Hospitalization and Death in Postmenopausal Women: A Collaborative Meta-Analysis of Randomized Controlled Trials[†]

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Abstract

Calcium supplementation, particularly with vitamin D has been an approved public health intervention to reduce fracture risk. Enthusiasm for this intervention has been mitigated by meta-analyses suggesting calcium supplementation with or without vitamin D increase myocardial infarction (MI) risk; however concern has been raised over the design of these meta-analyses. We therefore undertook a meta-analysis of randomized controlled trials with placebo or no-treatment control groups to determine if these supplements increase all-cause mortality and coronary heart disease (CHD) risk including: MI, angina pectoris and acute coronary syndrome, and chronic CHD verified by clinical review, hospital record or death certificate in elderly women. The Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE databases were searched from January 1, 1966 to May 24, 2013 for potentially eligible studies, reference lists were checked, and trial investigators contacted where additional unpublished data was required. The search yielded 661 potentially eligible reports of which 18 met the inclusion criteria and contributed information on 63,563 participants with 3,390 CHD events and 4,157 deaths. Two authors extracted the data independently with trial data combined using random-effects meta-analysis to calculate the relative risk (RR). Five trials contributed CHD events with pooled relative RR of 1.02 (95% CI, 0.96-1.09; P = 0.51). Seventeen trials contributed all-cause mortality data with pooled RR of 0.96 (95%CI, 0.91-1.02; P = 0.18). Heterogeneity among the trials was low for both primary outcomes (I^2 = 0%). For secondary outcomes the RR for MI was 1.08; 95% CI, 0.92-1.26; P = 0.32, angina pectoris and acute coronary syndrome 1.09; 95% CI, 0.95-1.24; P = 0.22 and chronic CHD 0.92; 95% CI, 0.73-1.15; P = 0.46. In conclusion, current evidence does not support the hypothesis that calcium supplementation with or without vitamin D increase coronary heart disease or all-cause mortality risk in elderly women.

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Introduction

A recent Institute of Medicine review of the scientific literature concluded that available scientific evidence supports a key role of calcium and vitamin D in the maintenance of skeletal health and recommended a daily intake of 1.2 g of calcium and 800 IU of vitamin D in elderly women (1). To meet these requirements calcium supplements with or without vitamin D are being widely used by elderly women (2). However a meta-analysis of randomized controlled trials (RCTs) has reported that calcium supplementation alone increases the risk of myocardial infarction by 27% (3). These authors then updated the previous report by including a number of RCTs of calcium supplements with vitamin D and concluded that these supplements increased the risk of myocardial infarction by 21% (4). Concerns regarding the approach taken in these meta-analyses have been raised (5).

Myocardial infarction is only one of several clinical presentations of coronary artery disease and is best captured using the international classification of disease (ICD) coronary heart disease (CHD) classification codes I20-I25 (6), which are a standard reporting category used by the American Heart Association (7). This category comprises of myocardial infarction, angina pectoris and acute coronary syndrome and chronic coronary heart disease. CHD begins with pathological changes to the endothelium due to biochemical or inflammatory stimuli that leads to increased permeability to monocytes and low density lipoproteins, endothelial and smooth muscle cell proliferation and extracellular matrix deposition, leading to atheromatous "plaques" on the endothelial surface (8,9). These plaques lead to clinical symptoms by either stenosis (stable angina pectoris and chronic coronary heart disease), or thrombi partially interrupting blood flow (unstable angina pectoris and acute coronary syndrome) or permanently interrupting blood flow (myocardial infarction) and are the primary cause of cardiovascular deaths in the US (7). Given coronary artery disease is the suggested mechanism of adverse effects of calcium supplementation CHD was a primary outcome of this study. Additionally all-cause mortality was a primary outcome as calcium supplements with vitamin D have been suggested to reduce death (10,11) and if this increased survival in the supplemented group is from causes other than CHD, for example increased cancer survival, the consequence may be an apparent increased risk of heart disease events.

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Other important considerations when addressing this issue include the gender specific differences in the epidemiology of coronary heart disease, verification of events by clinical review, hospital record or death certificate and the inclusion of all available RCTs of calcium supplementation with vitamin D. To date, no RCTs of calcium supplementation with or without vitamin D have had primary cardiovascular endpoints, and retrospective analyses of existing RCTs provide the highest level of evidence currently available. We therefore undertook a collaborative meta-analysis of published and unpublished data addressing each of these considerations to determine whether calcium supplementation with or without vitamin D increased coronary heart disease risk in elderly women.

Methods

Literature search

Randomized controlled trials of calcium supplementation with or without vitamin D were identified through Cochrane Central Register of Controlled Trials (1970 to 2013), MEDLINE (1966 to 2013), EMBASE (1974 to 2013) and reference lists. Additionally, studies identified from reviews and meta-analyses and their reference lists were included. The last update of the search was performed on 24 May 2013. Two search strategies were used. The preliminary search was limited to: human; randomised controlled trial published in the English language for trials meeting the inclusion criteria, intervention terms, "calcium", calcium supplementation", "vitamin D", "ergocalciferol", "calcifediol", "cholecalciferol", calcitriol" and outcomes terms including "vascular disease", "cardiovascular disease", "myocardial infarction", "coronary artery disease", "coronary heart disease" "mortality" or "death". An example search strategy is presented in Supplemental Table 1. After the initial search additional searches were performed using combinations of the intervention terms without outcome terms because some trials did not report cardiovascular or mortality outcomes as primary endpoints or search keywords. The process for selecting studies for inclusion in the review was as follows: merge search results using EndNote; remove duplicate records of the same report; retrieve the abstracts of the potentially relevant reports; link together multiple reports of the same study and exclude studies that were less than one year duration, studies where the mean age of the cohort was less than 50 years or studies that were not

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randomized controlled trials. During this abstract review studies that had both female and male participants, did not provide enough information to include or exclude and those that did not report all-cause or cardiovascular outcomes in the abstract were included for a full review of eligibility. Authors were contacted where additional data was required.

Trial selection

We included individual or cluster randomized controlled trials which compared calcium supplementation with or without vitamin D with a placebo or control group. Inclusion criteria were randomized controlled trials with a mean cohort age over 50 years where the groups differed only be calcium supplementation with or without oral vitamin D or calcium supplementation with or without vitamin D with a factor unlikely to affect coronary heart disease. Observational studies, trials with a dose lower than 0.5 g of calcium per day, trials where groups differed by factor that may be considered to mediate cardiovascular disease, trials with a mean cohort age less than 50 years, or trials with duration less than one year were excluded. Two authors (RLP, JRL) examined the full-text reports for compliance with eligibility criteria, corresponded with study investigators to clarify study eligibility if required and made final decisions on study eligibility and inclusion. Disagreements were resolved by discussion until a consensus was reached. All trials reporting coronary heart disease and / or all-cause mortality could be analyzed by intention to treat (Table 1).

Quality assessment

Quality and risk of bias was assessed using the Risk of Bias Tool developed by the Cochrane collaboration (12). Two authors (JRL and SRB) assessed trial quality and risk of bias including: random sequence generation (for assessing selection bias), allocation concealment (for assessing selection bias), blinding of participants and personnel (for assessing performance bias), blinding of outcome assessment (for assessing detection and mortality bias), incomplete outcome data addressed (for assessing attrition bias) and selective reporting (for assessing reporting bias).

Outcome measures

Consistent with the International Classification of Diseases coding and the American Heart Association guidelines for reporting coronary heart disease events, the pre-specified primary outcomes were coronary heart

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disease (ICD-10 codes I20-25),(6,7) and all-cause mortality. Secondary outcomes were myocardial infarction, angina pectoris including acute coronary syndrome and chronic coronary heart disease. Only studies reporting outcomes verified by clinical review, hospital discharge record or death certificate were included in the meta-analysis.

Data collection

Publications, trial design, patient characteristics, interventions and outcome data were independently extracted in duplicate (JRL and SRB). If studies used more than one control or intervention group, data on pairs of comparable test articles were collected e.g. Grant et al. (13) had two intervention arms: calcium vs. placebo and calcium with vitamin D vs. vitamin D alone. For studies that reported outcomes in men and women trial investigators were invited to participate in the meta-analysis by providing data for women only. The final protocol is available at http://boneandvascularresearch.org.au/publications.

Statistical analysis

Standard random-effects meta-analysis using Cochrane Review Manager (RevMan) computer program, version 5.2, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012 was undertaken to estimate the pooled relative risk (RR). All tests were two-tailed, and $P < 0.05$ was considered significant for the primary outcomes. *Post hoc* power calculations determined that the meta-analysis had 80% power to detect relative risk changes of 10% for coronary heart disease, 9% for all-cause mortality and 17% for myocardial infarction indicating sufficient power to detect the previously reported 24-31% increase in MI risk (3,4). Analyses were dichotomized by formulation of calcium supplements, calcium supplementation alone compared to calcium plus vitamin D, mean age of cohort (< 70 years and ≥ 70 years), duration of treatment (< 3 year, ≥3 years), trials randomized by individual versus trials randomized by cluster; and calcium dose (< 1 g/day and ≥ 1 g/day). Finally we restricted analyses to large trials (≥ 1000 participants) versus smaller trials (< 1000 participants), and trials with a low risk of bias (below the median risk of bias) versus trials with a high risk of bias (above the median risk of bias)(14). The robustness of the results was tested by repeating the analysis using different measures of effect size (risk ratio, odds ratio etc.) and different statistical models (fixed-effect and random-effects models). For secondary outcomes the Bonferroni multiple testing corrections for 3 tests were applied (P

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< 0.0167). For pre-specified subgroup and sensitivity tests the Bonferroni multiple testing corrections for 24 tests were applied (P < 0.002). All P values presented are uncorrected for multiple testing. Heterogeneity was identified by visual inspection of the forest plots and by using a standard chi squared test with a significance level of 0.1, in view of the low power of this test. We specifically examined heterogeneity by employing the I^2 statistic which quantifies inconsistency across studies to assess the impact of heterogeneity on the meta-analysis(15,16), where an I^2 statistic was categorized as 25-49% (low), 50-74% (moderate), ≥ 75% (high)(12). When heterogeneity was detected, we attempted to determine possible reasons by examining individual study and subgroup characteristics. Publication bias was assessed using funnel plots.

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Results

We identified 9,393 reports during literature and reference searches of which 661 were potentially eligible and underwent title and abstract review (Figure 1). After further evaluation, 21 potentially eligible studies remained; however, investigators of two studies that could contribute data in 517 women for all-cause mortality outcomes did not respond to requests for additional unpublished data (17,18) while investigators from a third study did not agree to contribute either cardiovascular or all-cause mortality data in 258 women (19). Thus, there were missing data for 775 / 62,900 (1.2%) of participants for all-cause mortality outcomes and 258 / 48,718 (0.5%) for coronary heart disease outcomes. Of the 18 studies included in the final analyses, 13 trials provided published data while five trials provided unpublished data (13,20-23). Overall the studies contributed data on 63,564 participants, while the median year of publication was 2005 (range 1994 to 2012).

Five trials of 48,460 participants provided data on coronary heart disease events and its subcategories while two additional trials of 2,651 participants contributed only myocardial infarction data (23,24). Of trials contributing heart disease events, two trials used primary cause of death from death certificates (13,22), 1 trial used linked hospitalization records (21), 1 trial used linked hospitalization and mortality records (20) and 3 trials collected self-reported data which was then verified by a clinician(s) (25-27).

Coronary heart disease (Figure 2)

No analyses reached nominal levels of significance ($P < 0.05$) for any coronary heart disease outcomes. Five studies contributed data on coronary heart disease hospitalization and death in 48,460 women. There were 1,720 / 24,284 (7.1%) coronary heart disease events in the calcium with or without vitamin D group compared to 1,670 / 24,176 (6.9%) in the control group (pooled RR 1.02, 95% CI, 0.96-1.09; P = 0.51) (Figure 2). There was no heterogeneity between studies (I^2 statistic = 0%) and no evidence of publication bias (Supplemental Figure 1). For coronary heart disease deaths, there were 307 / 24,284 (1.3%) in the calcium with or without vitamin D group compared to 297 / 24,176 (1.2%) in the control group (pooled RR 1.04, 95% CI, 0.88-1.21; P = 0.67 with no heterogeneity [I^2 statistic = 0%]).

All-cause mortality (Figure 3)

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No analyses reached nominal levels of significance (P < 0.05) for all-cause mortality. Seventeen studies contributed all-cause mortality data in 62,383 participants. There were 2,053 / 31,108 (6.6%) deaths in the calcium with or without vitamin D group compared to 2,104 / 31,275 (6.7%) in the control group (pooled RR 0.96, 95% CI, 0.91-1.02; P = 0.18). There was no heterogeneity between studies (I^2 statistic = 0%) and no evidence of publication bias (Supplemental Figure 1). When all-cause mortality analyses were restricted to the 7 studies contributing coronary heart disease data a similar pooled relative risk to the overall analysis was observed: RR = 0.96 (95% CI, 0.90-1.03; P = 0.26).

Secondary outcomes (Figure 4)

No analyses reached nominal levels of significance (P < 0.05) for any secondary outcomes so multiple testing corrections were not applied. Between 4 and 7 studies contributed data on between 48,033 to 51,111 participants for the pre-specified secondary outcomes: myocardial infarction, angina pectoris with acute coronary syndrome and chronic coronary heart disease. There was no increased risk in calcium treated patients for any secondary outcome (myocardial infarction: RR = 1.08 [95% CI, 0.93-1.25; P = 0.32]; angina pectoris: RR = 1.09 [95% CI, 0.95-1.24; P = 0.22]; chronic coronary heart disease: RR = 0.92 [95% CI, 0.73-1.15; P = 0.46]) with little heterogeneity between studies for myocardial infarction or angina pectoris (I^2 statistic = 8% and 0% respectively). For chronic coronary heart disease there was low heterogeneity (I^2 statistic = 38%). There was no evidence of publication bias as determined using funnel plots (Supplemental Figure 1).

Subgroup analyses (Figure 5 and Supplementary Table 2)

The detailed subgroup and sensitivity analyses are shown in Supplementary Table 2. No analyses reached nominal levels of significance (P < 0.05) for any secondary outcomes so multiple testing corrections were not applied. The relative risk for coronary heart disease varied from 1.00 (5 trials) to 1.81 (1 trial), whereas the pooled relative risk in subgroup analyses for all-cause mortality varied from 0.92 (6 and 9 trials respectively) to 1.38 (3 trials). Additional *post hoc* analyses were performed excluding the Women's Health Initiative (WHI) data (Supplementary Table 2), and including only the data in participants not taking personal supplements at baseline (28) in analyses of RCTs of calcium with vitamin D (Figure 5), with similar results. Further *post hoc* analysis using subgroup data from the WHI data in participants not using personal calcium supplementation at randomization (4) provided similar results (results not shown). The robustness of all results was tested by

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repeating the analyses using different measures of effect size (risk ratio, risk difference or odds ratio) and different statistical models (fixed-effect model and random-effects model) with no substantial change to the overall results for primary outcome, secondary outcome or subgroup and sensitivity analyses (results not shown).

Quality assessment

Details of the quality assessment and risks of bias for each study are provided in Supplemental Figure 2. Six of the 18 trials were open label or cluster randomized trials and thus were at a higher risk of performance and detection bias. The issue of the unit-of-analysis arising from including cluster-randomized trials was not specifically addressed. While including cluster randomized trials does not bias the estimates, it may increase the chance of a false positive finding. Since no significant findings were identified there is little need to account for the unit-of-analysis issue; indeed excluding cluster randomized trials and open label trials did not change the overall results (Supplementary Table 2).

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Discussion

To date, randomized controlled trials of calcium supplementation with or without vitamin D have not been specifically designed to include primary cardiovascular endpoints, so retrospective analyses of existing RCTs currently provide the highest level of evidence available. We therefore undertook a collaborative meta-analysis of both published and unpublished data in elderly women alone using coronary heart disease and its common clinical manifestations verified by clinical review, hospital record or death certificate to determine the safety of these commonly used supplements. The findings that calcium supplementation with or without vitamin D in elderly women did not increase coronary heart disease or all-cause mortality or the separate secondary outcomes of myocardial infarction, angina and acute coronary syndrome and chronic coronary heart disease verified by clinical review, hospital record or death certificate, are reassuring.

The overall relative risk for calcium supplements with or without vitamin D for myocardial infarction was 1.08 with 95% confidence intervals of 0.93-1.25. These confidence intervals are sufficiently broad that we cannot specifically exclude the 21% increase in myocardial infarction risk reported previously (4), however increases of this magnitude remain unlikely. Importantly in elderly women taking calcium supplementation with vitamin D, who form the majority of the participants in this meta-analysis, there were consistently null effects of the combination of these supplements on any verified coronary artery disease manifestations, including myocardial infarction, before and after excluding participants in the WHI study taking personal calcium supplementation at baseline. This contrasts with the previous meta-analysis that reported a 21% increase in myocardial infarction risk (4) based on a mix of self-reported and verified myocardial infarctions in men and women, which only included data from 3 trials with fewer participants and events than the current meta-analysis. Therefore to date existing evidence does not support the concept that calcium supplements with vitamin D increase the risk of coronary artery disease or its clinical manifestations including myocardial infarction, angina and acute coronary syndrome and chronic coronary heart disease. Given that we did not include randomized controlled trials where participants did not suffer any coronary heart disease events, relative risks presented in the meta-analysis are likely to inflate any “actual” risks, so our findings are unlikely to be due to a Type II error.

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However the sensitivity analysis showing an increased signal for myocardial infarction in women receiving calcium supplementation alone needs careful consideration despite being non-significant. It should be noted that the level of evidence for harm in this subgroup analysis is low as these estimates were based on only 139 myocardial infarctions in 6,333 participants compared to the estimates of calcium supplements with vitamin D based on 1,006 myocardial infarctions in 45,796 participants. Furthermore, given calcium monotherapy is no longer recommended for the maintenance of bone health in the elderly due to its lower anti-fracture efficacy, our findings suggest calcium supplements should always be administered with vitamin D given the higher level of evidence for its safety profile.

Regarding gender effects, men have a substantially higher risk of heart disease (7) and thus contribute more events. Recent data also suggest that men may respond differently to calcium supplementation than women. A large observational cohort study (29) reported an interaction between gender and calcium supplementation for the risk of CVD death, with calcium supplementation increasing the risk of CVD death in men, but not women, while a recent meta-analysis of RCTs of calcium or vitamin D supplementation reported that men may experience more harmful effects of calcium or vitamin D supplementation than women (30). Despite the majority of trial participants being elderly women, previous analyses have had significantly more elderly men in the calcium supplemented groups with no adjustment for gender in the analyses (3). We addressed this issue by seeking unpublished data from trial investigators for women only as any analysis in men would be underpowered to detect clinically meaningful differences in risk.

Whilst the convention for RCTs is not to apply a multiple testing correction when assessing adverse events to identify potential unrecognised side-effects or to determine the robustness of the findings in subgroup analyses, multiple testing corrections are used in meta-analyses to assess the robustness of the findings particularly as significant findings based on a 0.05 nominal level of statistical significance would be expected for every 20 tests performed. However given that no tests of the hypotheses reached even a nominal level of significance ($P < 0.05$) this issue did not affect our findings and provides reassurances that the null findings are sufficiently robust.

To date no mechanism(s) of calcium supplementation increasing cardiovascular disease risk has been identified. Manson et al. (31) reported that in a cross-sectional study of the Women's Health Initiative after 7

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years of supplementation with calcium and vitamin D that there was no effect on coronary artery calcified plaque burden. While an ancillary study of 1,103 women from the CAIFOS RCT found no effects of calcium supplementation on subclinical carotid atherosclerosis or common carotid artery intimal-medial thickness (32). Similarly Wang et al. (33) reported no effect of calcium supplementation on vascular calcification in either men or women. While a recent publication by Burt et al. (34) suggested that calcium supplementation reduces arterial wave reflection and a marker of myocardial perfusion and stated "*If maintained long-term, these changes would be expected to reduce cardiovascular risk.*". However despite these null findings further work is needed to investigate other potential biological mechanisms.

Observational studies have yielded conflicting findings regarding the safety or calcium supplementation with cardiovascular disease. Two large studies have identified reduced risk of CVD in participants using calcium supplements (28,35) while calcium supplementation has also been associated with a reduced risk of all-cause mortality in women (35,36). However other studies have failed to find any association (37) or have found calcium supplement use were associated with increased risk of myocardial infarction (38) and CHD (39). More recently, a very large study by Xiao et al. (29) in 388,229 men and women reported an interaction between calcium supplementation and gender for CVD death with men, but not women, using calcium supplements at increased risk of cardiovascular death (men >1 vs. 0 g/d RR 1.20; 95% CI, 1.05-1.36) supporting the concept that men may respond differently to supplementation to women.

While food-derived calcium is the optimal source to achieve the recommended dietary intake (RDI) of calcium, in cases where this RDI cannot be reached from food sources alone the use of long-term calcium supplementation with vitamin D in older women should be considered, given the beneficial effects on falls (1), bone mineral density and fracture outcomes (40) and all-cause mortality (10,11). However, given the uncertainty by patients and clinicians alike, further large well-designed randomized controlled trials of calcium supplementation with vitamin D that include verified bone and cardiovascular outcomes are urgently needed to address this issue.

Finally although it is inherent in randomized controlled trial methodology to study and report on efficacy and safety of the intervention, the trials reported were not necessarily specifically designed to assess beneficial or adverse effects of supplementation on coronary heart disease outcomes. With this limitation in

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mind, we conclude that when elderly women cannot meet the recommended daily intake of calcium through the diet alone, calcium supplementation with vitamin D does not appear to increase the risk of coronary heart disease or all-cause mortality. The safety of these supplements in elderly men and younger women remains unknown because studies of these populations are too small to provide clear answers.

Author Contributions:

Study concept and design: All authors. *Acquisition of data:* JRL, SRB, LR, JSC, JMS, JML, LM, RLP. *Analysis and interpretation of data:* All authors. *Drafting of the manuscript:* All authors. *Critical revision of the manuscript for important intellectual content:* All authors. *Statistical analysis:* JRL, RLP. *Obtained funding:* JRL. *Administrative, technical, or material support:* JRL, SRB. JRL had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1. Study characteristics for the 18 studies contributing data to the meta-analysis

Study	Intervention and control dose (g) or IU per day	Outcomes reported	Trial design	No. calcium group / No. control group	Mean age of cohort (years)	Duration (years)
Bæksgaard 1998(41)	I1: Calcium carbonate 1 g and 560IU of vitamin D3 I2: Calcium carbonate 1 g, 560IU of vitamin D3 and multivitamin supplement C1: Placebo	Mortality	RCT	I1: 80 I2: 80 C1: 80	63	2
Bonnick 2007(42)	I1: Calcium carbonate 1 g and Alendronate 10 mg/day I2: Calcium carbonate 1 g C1:Alendronate 10 mg/day *All participants were on multivitamin capsules containing 400IU of vitamin D3 + dietary calcium ≥ 0.8 g.	Mortality	RCT	I1: 282 I2: 138 C1: 281	66	2
Brazier 2005(43)	I1: Calcium carbonate 0.5 g and 400IU of vitamin D3 C1: Placebo	Mortality	RCT	I1: 95 C1: 97	75	1
Chailurkit 2010(44)	I1: Calcium carbonate 0.5 g C1: Placebo	Mortality	RCT	I1: 201 C1: 196	66	2
Chapuy 1992(45)	I1: Tricalcium phosphate 1.2 g and 800IU of vitamin D3 C1: Placebo	Mortality	RCT	I1: 1,634 C1: 1,636	84	1.5
Chapuy 2002(46)	I1: Tricalcium phosphate 1.2 g and 800IU of vitamin D3 (combined) I2: Tricalcium phosphate 1.2 g and 800IU of vitamin D3 (separate) C1: Placebo	Mortality	RCT	I1: 199 I2: 194 C1: 190	85	2
Grant 2005(13)	I1: Calcium carbonate 1 g I2: Calcium carbonate 1 g and 800IU of vitamin D3 C1: Placebo C2: 800IU of vitamin D3	Mortality, CHD	Factorial RCT	I1: 1,113 I2: 1,104 C1: 1,128 C2: 1,136	77	24-62 months
Harwood 2004(47)	I1: Calcium carbonate 1g and 800IU of vitamin D2 C1: No treatment	Mortality	RCT	I1: 39 C1: 37	81	1
Jackson	I1: Calcium carbonate 1 g and 400IU of vitamin D3	Mortality,	RCT	I1: 18,176	62	7

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2006(27,28,48)	C1: Placebo	CHD		C1: 18,106		
Krieg 1999(49)	I1: Calcium carbonate 1 g and 880IU of vitamin D3 C1: No treatment	Mortality	Open-label RCT	I1: 124 C1: 124	85	2
Lappe 2007(23,25)	I1: Calcium citrate 1.4 g or calcium carbonate 1.5g I2: Calcium citrate 1.4 g or calcium carbonate 1.5g and 1000IU of vitamin D3 C1: Placebo	MI	RCT	I1: 446 I2: 446 C1: 288	67	4
Larsen 2004(21)	I1: Calcium carbonate 1 g and 400IU of vitamin D3 C1: No treatment	Mortality, CHD	Cluster RCT	I1: 2,983 C1: 2,788	75	3
Porthouse 2005(50)	I1: Calcium carbonate 1 g and 800IU of vitamin D3 and general lifestyle advice C1: General lifestyle advice	Mortality	Open-label RCT	I1: 1,321 C1: 1,993	77	18–42
Prince 2006(20,51,52)	I1: Calcium carbonate 1.2 g I2: Calcium carbonate 1.2 g and 1000IU of vitamin D2 C1: Placebo	Mortality, CHD	RCT	I1: 730 I2: 39 C1: 730	75	5
Reid 2006(24,26)	I1: Calcium citrate 1 g C1: Placebo	Mortality, MI	RCT	I1: 732 C1: 739	74	5
Riggs 1998(53)	I1: Calcium citrate 1.6 g C1: Placebo	Mortality	RCT	I1: 119 C1: 117	66	4
Salovaara 2010(54)	I1: Calcium carbonate 1 g and 800IU of vitamin D3 C1: No treatment	Mortality	Open-label RCT	I1: 1,586 C1: 1,609	67	3
Sambrook 2012(22)	I1: Calcium carbonate 0.6g and sun exposure C1: Sun exposure C2: No treatment	Mortality, CHD	Cluster RCT	I1: 139 C1: 137 C2: 151	87	1

Abbreviations; IU = International units; RCT = Randomised controlled trial; CHD = Coronary heart disease; MI = myocardial infarction only; I = intervention and C = control.

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Figure legend

Fig. 1. Flow diagram of the search strategy.

Fig. 2. Random-effects estimates of effect of calcium supplementation with or without vitamin D for the risk of coronary heart disease compared to no calcium. For Grant et al. (2005), events were reported in those who received calcium cf. placebo (Ca) and calcium plus vitamin D cf. vitamin D only (CaD). M-H: Mantel-Haenszel, this method estimates the amount of between-study variation by comparing each study's result with a Mantel-Haenszel fixed-effect meta-analysis result.

Fig. 3. Random-effects estimates of effect of calcium supplementation with or without vitamin D for the risk of all-cause mortality compared to no calcium. For Grant et al. (2005), events were reported in those who received calcium cf. placebo (Ca) and calcium plus vitamin D cf. vitamin D only (CaD). M-H: Mantel-Haenszel, this method estimates the amount of between-study variation by comparing each study's result with a Mantel-Haenszel fixed-effect meta-analysis result.

Fig. 4. Random effects estimates of calcium supplementation with or without vitamin D for a) myocardial infarction, b) angina pectoris and acute coronary syndrome and c) chronic coronary heart disease compared to no calcium. For Grant et al. (2005), events were reported in those who received calcium cf. placebo (Ca) and calcium plus vitamin D cf. vitamin D only (CaD). M-H: Mantel-Haenszel, this method estimates the amount of between-study variation by comparing each study's result with a Mantel-Haenszel fixed-effect meta-analysis result.

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Fig. 5. Sensitivity analyses based on type of supplementation. *Post hoc subgroup analysis of the Women's Health Initiative (WHI) in participants with no personal supplements at baseline (NPS) using the trial investigators internal dataset (28). M-H: Mantel-Haenszel, this method estimates the amount of between-study variation by comparing each study's result with a Mantel-Haenszel fixed-effect meta-analysis result.

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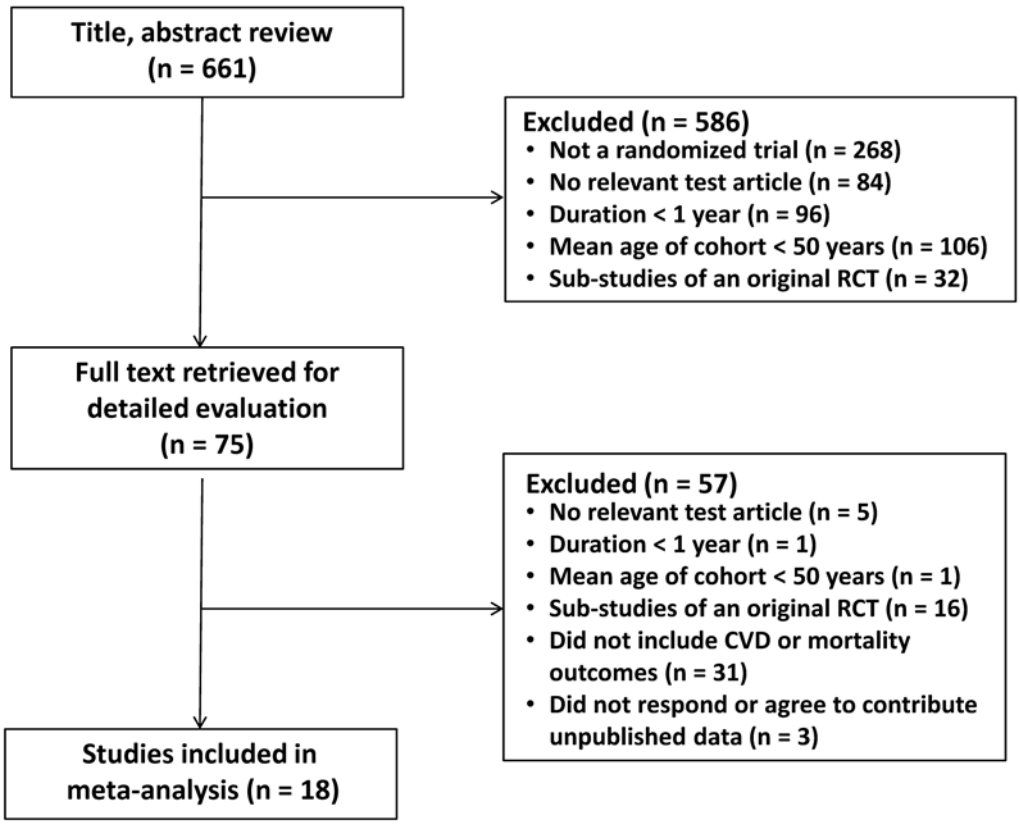

Figure 1

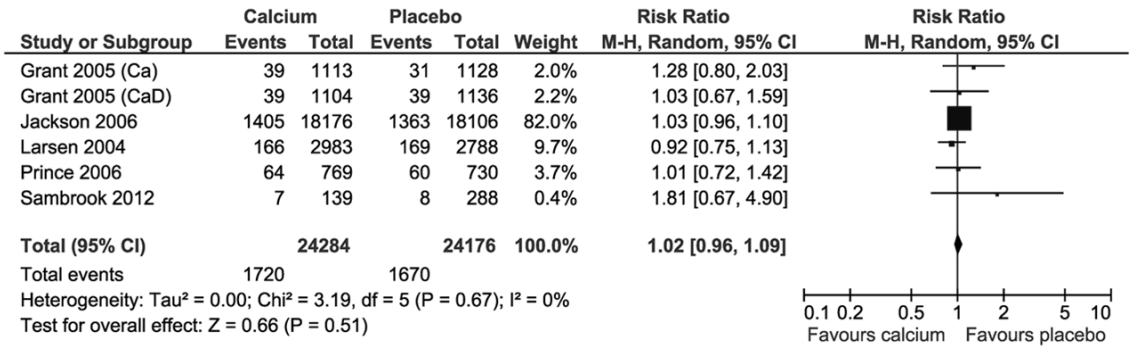

Figure 2

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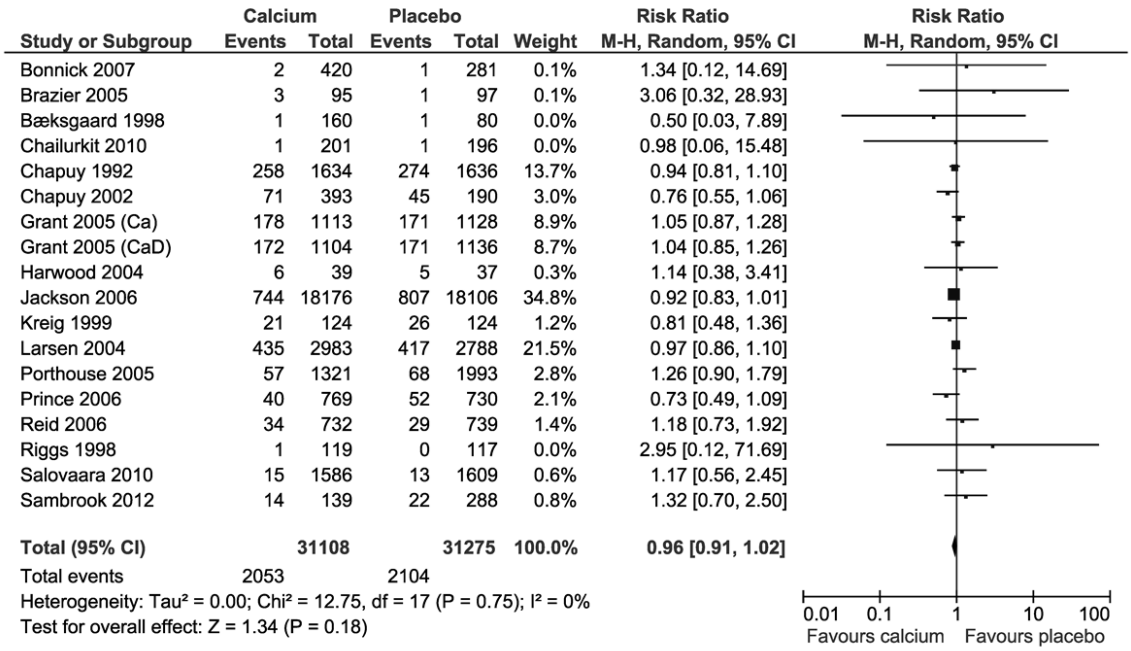

Figure 3

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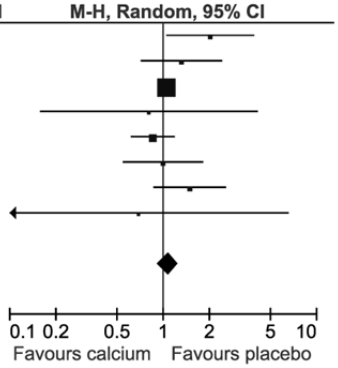
a) Myocardial Infarction

Study or Subgroup	Calcium Events	Calcium Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Grant 2005 (Ca)	26	1113	13	1128	4.7%	2.03 [1.05, 3.92]
Grant 2005 (CaD)	23	1104	18	1136	5.4%	1.31 [0.71, 2.42]
Jackson 2006	411	18176	390	18106	59.5%	1.05 [0.92, 1.20]
Lappe 2007	5	892	2	288	0.8%	0.81 [0.16, 4.14]
Larsen 2004	66	2983	72	2788	16.9%	0.86 [0.62, 1.19]
Prince 2006	21	769	20	730	5.6%	1.00 [0.54, 1.82]
Reid 2006	31	732	21	739	6.8%	1.49 [0.86, 2.57]
Sambrook 2012	1	139	3	288	0.4%	0.69 [0.07, 6.58]
Total (95% CI)		**25908**		**25203**	**100.0%**	**1.08 [0.93, 1.25]**
Total events	584		539			

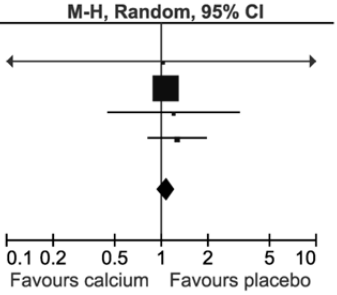
Heterogeneity: Tau² = 0.00; Chi² = 7.58, df = 7 (P = 0.37); I² = 8%
Test for overall effect: Z = 1.00 (P = 0.32)



b) Angina Pectoris and Acute Coronary Syndrome

Study or Subgroup	Calcium Events	Calcium Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Grant 2005 (Ca)	0	1113	0	1128		Not estimable
Grant 2005 (CaD)	1	1104	1	1136	0.2%	1.03 [0.06, 16.43]
Jackson 2006	404	18176	377	18106	89.1%	1.07 [0.93, 1.23]
Larsen 2004	9	2983	7	2788	1.8%	1.20 [0.45, 3.22]
Prince 2006	44	769	33	730	8.9%	1.27 [0.82, 1.96]
Total (95% CI)		**24145**		**23888**	**100.0%**	**1.09 [0.95, 1.24]**
Total events	458		418			

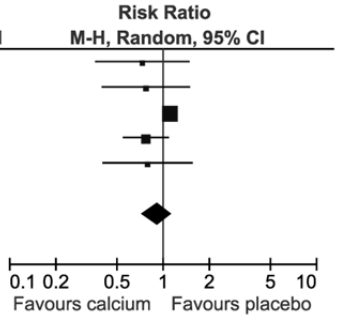
Heterogeneity: Tau² = 0.00; Chi² = 0.57, df = 3 (P = 0.90); I² = 0%
Test for overall effect: Z = 1.23 (P = 0.22)



c) Chronic Coronary Heart Disease

Study or Subgroup	Calcium Events	Calcium Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Grant 2005 (Ca)	13	1113	18	1128	8.5%	0.73 [0.36, 1.49]
Grant 2005 (CaD)	15	1104	20	1136	9.4%	0.77 [0.40, 1.50]
Jackson 2006	674	18176	607	18106	49.1%	1.11 [0.99, 1.23]
Larsen 2004	57	2983	69	2788	23.8%	0.77 [0.55, 1.09]
Prince 2006	15	769	18	730	9.1%	0.79 [0.40, 1.56]
Total (95% CI)		**24145**		**23888**	**100.0%**	**0.92 [0.73, 1.15]**
Total events	774		732			

Heterogeneity: Tau² = 0.02; Chi² = 6.40, df = 4 (P = 0.17); I² = 38%
Test for overall effect: Z = 0.74 (P = 0.46)



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Outcome	Trials (No. participants)	Risk Ratio, M-H, Random, 95% CI	P value
Coronary heart disease			
Overall	5 (48,460)	1.02 (0.96-1.09)	0.51
Calcium alone	3 (4,128)	1.15 (0.88-1.50)	0.30
Calcium with D	4 (45,062)	1.01 (0.95-1.08)	0.69
Calcium with D + WHI (NPS)*	4 (24,082)	0.95 (0.86-1.04)	0.23
All-cause mortality			
Overall	17 (62,383)	0.96 (0.91-1.02)	0.18
Calcium alone	7 (6,933)	1.03 (0.88-1.21)	0.68
Calcium with D	12 (56,180)	0.95 (0.89-1.01)	0.11
Calcium with D + WHI (NPS)*	12 (35,200)	0.97 (0.91-1.04)	0.41
Myocardial infarction			
Overall	7 (51,111)	1.08 (0.93-1.25)	0.32
Calcium alone	5 (6,333)	1.37 (0.98-1.92)	0.07
Calcium with D	5 (45,796)	1.03 (0.91-1.16)	0.65
Calcium with D + WHI (NPS)*	5 (24,816)	1.07 (0.90-1.26)	0.45

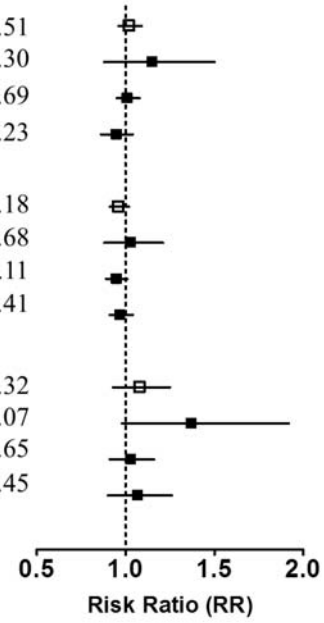

Figure 5