Subgroup analysis for the risk of cardiovascular disease with calcium supplements

Loretta T Radford, Mark J Bolland, Greg D Gamble, Andrew Grey and Ian R Reid

Bone and Joint Research Group, Department of Medicine, University of Auckland, Auckland, New Zealand.

Calcium supplements have been reported to increase the risk of myocardial infarction (MI). We wished to determine whether the effects of calcium supplements on cardiovascular risk vary across different population groups. We modeled the effect of calcium (with or without vitamin D) on the time to incident cardiovascular events in pre-specified subgroups based on age, dietary calcium intake, body mass index, smoking history, history of hypertension, diabetes and prevalent cardiovascular disease, using interaction terms in Cox proportional hazards models in two randomized controlled trial data sets—our re-analysis of the Women's Health Initiative Calcium and Vitamin D study (WHI CaD), and our pooled patient-level meta-analysis of trials of calcium supplements with or without vitamin D. For women in WHI CaD not taking calcium supplements at randomization (n=16,718), we found no significant interactions between treatment allocation, the risk of MI, stroke or coronary revascularization, or any of the baseline variables. In the pooled patient-level data set of six trials of calcium with or without vitamin D (n=24,869), there were also no significant interactions between treatment allocation, risk of MI or stroke, and any of the baseline variables. We found no evidence that the increased cardiovascular risk from calcium supplements differs across varying patient subpopulations. These findings suggest that targeted prescription of calcium supplements to specific population subgroups, such as younger people and those with low dietary calcium intake, should not be endorsed.

Introduction

Calcium supplements have been widely used for the treatment and prevention of osteoporotic fractures, but recently their cardiovascular safety has been questioned. A secondary analysis of the Auckland Calcium Study showed a 43% increase in the rate of cardiovascular events in women randomized to 1 g daily calcium (as citrate).1 In a subsequent meta-analysis of 11 randomized, placebo-controlled trials of calcium supplements with nearly 12,000 participants, calcium increased the risk of myocardial infarction (MI) by 27–31%.2 In the Women’s Health Initiative Calcium and Vitamin D study (WHI CaD), calcium co-administered with vitamin D (CaD) increased the risk of MI by 22% in women who were not taking personal, non-protocol calcium supplements at randomization.3 Figure 1 shows that the results from the meta-analysis of calcium monotherapy and the re-analysis of WHI CaD were similar, including the longer latency for the development of the effect on stroke. Because of this similarity in outcomes, we pooled the data sets to produce a meta-analysis of trials of calcium supplements with or without vitamin D. Thirteen trials were included, involving nearly 30,000 participants. Calcium increased the risk of MI by 25% and stroke by 15–20%.3

An important question is whether the increased cardiovascular risk from calcium supplements is consistent across the population, or whether some patient groups are at greater risk. There is already some evidence suggesting this. For example, in the meta-analysis of trials of calcium monotherapy, there was an interaction between dietary calcium intake and the risk of MI with calcium supplements.2,4 In the group with dietary calcium intake above the median (805 mg day$^{-1}$), there was an increased risk of MI with calcium supplements, but there was no dose–response relationship in an analysis based on quintiles of dietary calcium intake. In the primary analysis of WHI CaD, there was an interaction between body mass index (BMI) and the risk of MI or death from coronary heart disease (CHD), with an elevated risk of this composite end point with CaD only in women with BMI <30 kg m$^{-2}$.5 In a 5-year randomized controlled trial of calcium supplements, Lewis et al.6 reported that calcium supplements reduced the risk of atherosclerotic vascular disease in women with known atherosclerotic vascular disease at baseline.

To explore these contrasting findings, we investigated whether the effects of calcium supplements on the risk of MI and stroke vary across different subgroups in our re-analysis of WHI...
CaD, or in the pooled patient-level data set of trials of calcium supplements with or without vitamin D. Detailed subgroup analyses have not previously been carried out in these data sets. WHI CaD had a broader range of baseline data than the pooled data set, allowing for a greater variety of subgroups to be assessed.

Results

Table 1 depicts selected baseline characteristics of women in WHI CaD who were not using calcium supplements at randomization. There were no significant differences between the groups. Figures 2–4 show the interactions between WHI CaD allocation and baseline characteristics for the risk of MI, stroke and coronary revascularization. For each of these end points, we found no evidence of significant interactions between treatment allocation and any of the baseline variables.

In the complete WHI CaD data set, there was a significant interaction between allocation to CaD, BMI and the composite end point of MI or CHD death. In our analysis of women not taking calcium supplements at randomization, we found no statistically significant interactions between allocation to CaD, BMI, and either MI, stroke or coronary revascularization (Figures 2–4). As our findings differed from those of the primary WHI CaD analysis, we repeated our analyses in women using personal calcium supplements at randomization and found no evidence for interactions between calcium supplements and BMI, allocation to CaD or in the pooled patient-level data set of trials of calcium supplements with or without vitamin D. We found no evidence of a dose–response relationship. There was also no interaction between dietary calcium intake and the risk of MI with calcium supplements. The group with intake greater than the median of 805 mg day−1 had an increased risk of MI with calcium, whereas those with intake below the median had no alteration of risk. However, when the cohort was divided by quintile of dietary calcium intake, there was no evidence of a dose–response relationship. There was also no interaction between dietary calcium intake and the risk of stroke, or the composite cardiovascular end point with calcium. Therefore, we concluded

Table 1 Selected baseline characteristics of women in the Women's Health Initiative calcium and vitamin D study who were not taking calcium supplements at baseline

| Characteristic          | CaD (n = 8429) | Placebo (n = 8289) | P-value |
|-------------------------|---------------|-------------------|---------|
| Age (years)             |               |                   |         |
| Mean (s.d.)             | 62.9 (7.0)    | 62.9 (7.0)        | 0.91    |
| <60                     | 39            | 38                |         |
| 60–70                   | 43            | 44                |         |
| >70                     | 18            | 18                |         |
| Body mass index (kg m−2)|               |                   |         |
| Mean (s.d.)             | 29.4 (5.9)    | 29.4 (6.0)        | 0.80    |
| <25                     | 24            | 25                |         |
| 25–30                   | 36            | 34                |         |
| >30                     | 40            | 41                |         |
| Dietary calcium (mg day−1): |           |                   | 0.42    |
| Mean (s.d.)             | 804 (489)     | 798 (475)         |         |
| <500                    | 28            | 29                |         |
| 500–700                 | 21            | 21                |         |
| 700–900                 | 17            | 18                |         |
| 900–1100                | 12            | 12                |         |
| >1100                   | 21            | 20                |         |
| History of MI           | 2.3           | 2.0               | 0.26    |
| History of stroke       | 1.0           | 1.2               | 0.35    |

Abbreviations: CaD, calcium and vitamin D; MI, myocardial infarction. Data are mean (s.d.) or %.

In the pooled patient-level meta-analysis data set, the overall hazard ratio for time to incident MI for calcium with or without vitamin D was 1.25 (95% CI: 1.06–1.46; P = 0.0065) and for time to incident stroke was 1.19 (95% CI: 1.02–1.39; P = 0.026). There were no significant interactions between treatment allocation and age, gender, dietary calcium intake, smoking history, history of cardiovascular disease, diabetes mellitus or hypertension either for the risk of MI (Table 3) or for the risk of stroke (Table 4).

Discussion

In women in WHI CaD who were not taking calcium supplements at baseline and in the pooled patient-level meta-analysis of trials of calcium with or without vitamin D, we found no evidence for interactions between calcium supplements and age, gender, BMI, baseline dietary calcium intake, smoking status, previous history of cardiovascular disease, diabetes mellitus or history of hypertension for the risk of MI, stroke or coronary revascularization. Previously, in a meta-analysis of five studies of calcium monotherapy, we reported a significant interaction between dietary calcium intake and the risk of MI with calcium supplements. The group with intake greater than the median of 805 mg day−1 had an increased risk of MI with calcium, whereas those with intake below the median had no alteration of risk. However, when the cohort was divided by quintile of dietary calcium intake, there was no evidence of a dose–response relationship. There was also no interaction between dietary calcium intake and the risk of stroke, or the composite cardiovascular end point with calcium. Therefore, we concluded
that the evidence for a relationship between dietary calcium intake, calcium supplement use and cardiovascular risk was weak. The current study supports this conclusion: there was no significant interaction between dietary calcium intake (when assessed either by median intake or by quintiles of intake) and allocation to calcium with or without vitamin D for the risk of MI, stroke or coronary revascularization. Some, however, interpreted the previous findings as suggesting that the increased cardiovascular risk was related to the total calcium intake—the use of calcium supplements on the background of a high dietary calcium intake—and therefore that calcium supplements were safe for individuals with low calcium intake. The current study does not support this interpretation, as the hazard ratios for MI, stroke and coronary revascularization were similar across all quintiles of dietary calcium intake.

In the primary analysis of WHI CaD, Hsia et al. reported a significant interaction between BMI and the use of CaD for the risk of the composite end point of MI or CHD death, with an increased risk with CaD observed in women with BMI \(< 30\text{ kg m}^{-2}\). In contrast, we observed no interaction between CaD and BMI for the risk of MI in women in WHI CaD who did not use calcium supplements at randomization. However, in those women using non-protocol calcium supplements at randomization, there was a significant interaction between BMI, CaD and the risk of MI, with an inverse relationship between BMI and the risk of MI from CaD. In women with normal BMI \(< 25\text{ kg m}^{-2}\), the hazard ratio was 1.19, similar to the risk observed in women not taking personal calcium supplements at randomization, whereas overweight and obese women had no alteration of risk (hazard ratio 0.99) and a reduced risk (hazard ratio 0.76), respectively. This inverse relationship persisted after adjustment for traditional cardiovascular risk factors. It seems most likely that this finding is either due to chance or due to confounding by other unmeasured variables, rather than there being a true relationship between BMI and the risk of MI from CaD.

Lewis et al. reported that calcium supplements reduced the risk of an atherosclerotic vascular event during 5 years of follow-up in women who had a history of atherosclerotic vascular disease. This result should be treated with caution for several reasons. The composite outcome contained end points that may result from a wide number of pathogenetic processes unrelated to atherosclerosis, such as atrial fibrillation and congestive heart failure. All patient events were obtained from unadjudicated hospital discharge codes, and only the primary code for each admission was utilized, which is likely to have resulted in missed events. For example, there were 28 MIs identified from coding in 1460 women of mean age 75 years
followed for 5 years. Compared to other studies in our meta-
analysis of calcium monotherapy, this event rate was approximately half to one-third the rate in women of similar age in two studies, and similar to the rate in women who were on average 12–16 years younger in two other studies. The study lacked adequate power, either in the primary analysis or in subgroup analyses, to detect differences in event rates between the treatment groups of the magnitude observed in our meta-analyses. Finally, the authors did not follow recommendations for the reporting of subgroups in that they have reported hazard ratios and for single subgroups. The recommended approach is to report the results of interaction tests between subgroups (that is, the subgroups with or without atherosclerotic vascular disease at baseline) and only consider individual subgroup results if the interaction test is statistically significant. We did not confirm interactions between history of MI or stroke and the risk of cardiovascular events with calcium in WHI CaD.

Our study has some limitations. As we used the WHI limited-access clinical trials data set for our analysis, we are limited to the information available in this data set. Subgroup analyses increase the likelihood of detection of false-positive results and therefore significant results require cautious interpretation. However, we have not identified significant interactions in the current analysis. Lack of power is also potentially an issue when performing subgroup analyses, because the decrease in the number of relevant events in each group analyzed may result in a Type 2 error. The large number of events in the data set suggests that if such an error occurred, it is not likely to be clinically relevant.

In conclusion, calcium supplements with or without vitamin D are associated with an increased risk for MI and stroke, and this risk appears to apply across subgroups defined by important baseline characteristics. These findings suggest that targeted prescription of calcium supplements to specific population subgroups, such as younger people and those with low dietary calcium intake, should not be endorsed.

Materials and Methods

In brief, WHI CaD was a randomized, double-blind, placebo-controlled study of 1 g calcium/400 IU vitamin D daily in 36,282 post-menopausal women followed for an average duration of 7 years. Medical records related to self-reported medical events for MI, stroke and coronary revascularization were adjudicated centrally by physician adjudicators using

![Figure 4](https://example.com/figure4.png) Risk of coronary revascularization in women in the Women’s Health Initiative (WHI) calcium and vitamin D trial not using personal calcium supplements at randomization by treatment in subgroups defined by various baseline characteristics. Results are reported as hazard ratios with 95% confidence intervals (CI) (horizontal bar). The dotted vertical line represents the hazard ratio for the entire cohort (hazard ratio 1.15, 95% CI: 0.98–1.34, \( P = 0.09 \)).

| Subgroup | \( p \) value for interaction | Hazard Ratio for Coronary Revascularization (95% CI) |
|----------|-------------------------------|--------------------------------------------------|
| Age (y)  |                               |                                                  |
| < 60     |                               |                                                  |
| 60<70    |                               |                                                  |
| >70      |                               |                                                  |
| Dietary calcium (mg/d) |               |                                                  |
| < 500    |                               |                                                  |
| 500-699  |                               |                                                  |
| 700-899  |                               |                                                  |
| 900-1099 |                               |                                                  |
| ≥ 1100   |                               |                                                  |
| Body Mass Index (kg/m\(^2\)) |         |                                                  |
| < 25     |                               |                                                  |
| 25<30    |                               |                                                  |
| ≥ 30     |                               |                                                  |
| History of MI |                     |                                                  |
| Yes      |                               |                                                  |
| No       |                               |                                                  |
| Smoking history |                   |                                                  |
| Never    |                               |                                                  |
| Previous |                               |                                                  |
| Current  |                               |                                                  |

Table 2 Effect of BMI on the risk of MI and stroke with CaD in the WHI CaD Study, grouped by personal use of calcium supplements at randomization

|                        | No personal use of calcium | Any personal use of calcium |
|------------------------|----------------------------|----------------------------|
|                        | CaD, n (%) | Placebo, n (%) | HR (95% CI) | P-value for interaction | CaD, n (%) | Placebo, n (%) | HR (95% CI) | P-value for interaction |
| MI                     |            |                |              |                          |            |                |              |                          |
| BMI < 25               | 39 (1.9)   | 34 (1.6)       | 1.21 (0.76–1.93) | 0.78                      | 48 (1.6)   | 42 (1.3)       | 1.19 (0.79–1.82) | 0.049             |
| BMI 25–30              | 75 (2.5)   | 61 (2.1)       | 1.19 (0.84–1.67) |                          | 72 (2.1)   | 71 (2.0)       | 0.99 (0.71–1.39) |                          |
| BMI ≥ 30               | 95 (2.8)   | 73 (2.2)       | 1.21 (0.87–1.68) |                          | 60 (1.8)   | 83 (2.6)       | 0.76 (0.53–1.07) |                          |
| Stroke                 |            |                |              |                          |            |                |              |                          |
| BMI < 25               | 48 (2.4)   | 32 (1.6)       | 1.59 (0.99–2.54) | 0.22                      | 47 (1.5)   | 59 (1.8)       | 0.83 (0.56–1.23) | 0.73               |
| BMI 25–30              | 68 (2.3)   | 56 (2.0)       | 1.16 (0.81–1.66) |                          | 62 (1.8)   | 73 (2.1)       | 0.88 (0.62–1.24) |                          |
| BMI ≥ 30               | 80 (2.4)   | 74 (2.2)       | 1.07 (0.87–1.32) |                          | 47 (1.4)   | 78 (1.8)       | 0.78 (0.52–1.21) |                          |

Abbreviations: BMI, body mass index; CaD, calcium and vitamin D; CI, confidence interval; HR, hazard ratio. BMI in kg m\(^{-2}\).
standardized definitions, and all deaths were also centrally adjudicated. The primary analysis reported no effect of CaD on cardiovascular events, but 54% of participants were taking personal calcium supplements at randomization. We have therefore restricted our current analyses to women not taking personal calcium supplements at randomization. We obtained the WHI limited-access clinical trials data set from the National Heart Lung and Blood Institute. In a re-analysis of this data set, we found interactions between personal calcium supplement use and CaD for cardiovascular events. In women not using personal calcium supplements at randomization, CaD increased cardiovascular risk, whereas there was no alteration of risk in women already taking calcium supplements at randomization. We have therefore restricted our current analyses to women not taking personal calcium supplements at randomization.

For the meta-analysis of calcium with or without vitamin D, we searched Medline, Embase and the Cochrane Central Register of Controlled Trials for randomized placebo-controlled trials of calcium supplements used as monotherapy in March 2010. Eligible studies were randomized, placebo-controlled trials of calcium supplements (≥500 mg day⁻¹), with 100 or more participants of mean age more than 40 years, and a study duration of more than 1 year. Fifteen trials were eligible, six supplied trial-level data only and five supplied patient-level data. In these five trials, cardiovascular events were from unadjudicated self-reports (one study); verified events from hospital discharge data and adjudicated death certificates (one study); self-reports, hospital admissions and death certificates that were independently adjudicated by a cardiologist or neurologist (two studies). A systematic review identified two randomized, placebo-controlled trials of CaD with cardiovascular outcomes—WHI CaD and another small study. We updated the patient-level data set for trials of calcium monotherapy with placebo, with 100 or more participants of mean age more than 40 years, and a study duration of more than 1 year. Fifteen trials were eligible, six supplied trial-level data only and six supplied patient-level data. In these five trials, cardiovascular events were from unadjudicated self-reports (one study); verified events from hospital discharge data and adjudicated death certificates (one study); self-reports, hospital admissions and death certificates that were independently adjudicated by a cardiologist or neurologist (two studies). A systematic review identified two randomized, placebo-controlled trials of CaD with cardiovascular outcomes—WHI CaD and another small study.

Table 3 Risk of myocardial infarction by treatment allocation in subgroups in the patient-level meta-analysis data set

| Calcium/ CaD, n (%) | Placebo, n (%) | HR (95% CI) | P-value for interaction |
|---------------------|---------------|-------------|------------------------|
| Age (years)         |               |             |                        |
| < 60                | 45 (1.2)      | 32 (0.9)    | 1.28 (0.81–2.02)       | 0.62 |
| 60–70               | 108 (2.7)     | 95 (2.4)    | 1.10 (0.83–1.46)       |     |
| ≥ 70                | 199 (4.1)     | 152 (3.1)   | 1.37 (1.10–1.70)       |     |
| Gender              |               |             |                        |
| Male                | 38 (4.0)      | 32 (3.8)    | 1.22 (0.73–2.06)       | 0.73 |
| Female              | 314 (2.7)     | 247 (2.2)   | 1.28 (1.08–1.52)       |     |
| Dietary calcium     |               |             |                        |
| (mg day⁻¹)          |               |             |                        |
| < 400               | 63 (3.1)      | 59 (3.1)    | 1.19 (0.81–1.74)       | 0.39 |
| 400–600             | 80 (3.1)      | 74 (2.8)    | 1.05 (0.76–1.46)       |     |
| 600–800             | 63 (2.6)      | 45 (1.9)    | 1.52 (1.01–2.28)       |     |
| 800–1100            | 81 (2.8)      | 52 (1.9)    | 1.24 (0.85–1.80)       |     |
| ≥ 1100              | 65 (2.5)      | 49 (1.9)    | 1.32 (0.89–1.94)       |     |
| Dietary calcium     |               |             |                        |
| (mg day⁻¹)          |               |             |                        |
| < Median (737 mg day⁻¹) | 164 (2.6)   | 117 (1.9)   | 1.31 (1.02–1.67)       | 0.10 |
| > Median            | 188 (3.0)     | 162 (2.6)   | 1.23 (0.99–1.53)       |     |
| History of CVD      |               |             |                        |
| Yes                 | 50 (4.7)      | 49 (4.6)    | 1.03 (0.69–1.53)       | 0.32 |
| No                  | 133 (2.1)     | 100 (1.6)   | 1.31 (1.01–1.70)       |     |
| Smoking history     |               |             |                        |
| Never               | 126 (2.5)     | 103 (2.1)   | 1.20 (0.92–1.57)       | 0.89 |
| Previous            | 93 (2.4)      | 74 (2.0)    | 1.14 (0.83–1.57)       |     |
| Current             | 49 (4.0)      | 37 (3.2)    | 1.39 (0.88–2.18)       |     |
| Diabetes mellitus   |               |             |                        |
| Yes                 | 66 (7.8)      | 40 (4.9)    | 1.74 (1.15–2.65)       | 0.18 |
| No                  | 285 (2.4)     | 239 (2.1)   | 1.19 (1.00–1.42)       |     |
| History of hypertension |        |             |                        |
| Yes                 | 132 (4.1)     | 102 (3.1)   | 1.40 (1.07–1.82)       | 0.17 |
| No                  | 128 (1.9)     | 102 (1.6)   | 1.06 (0.81–1.38)       |     |

Table 4 Risk of stroke by treatment allocation in various subgroups in the patient-level meta-analysis data set

| Calcium/ CaD, n (%) | Placebo, n (%) | HR (95% CI) | P-value for interaction |
|---------------------|---------------|-------------|------------------------|
| Age (years)         |               |             |                        |
| < 60                | 25 (0.7)      | 24 (0.7)    | 1.01 (0.58–1.77)       | 0.57 |
| 60–70               | 102 (2.5)     | 87 (2.2)    | 1.19 (0.89–1.58)       |     |
| ≥ 70                | 236 (4.8)     | 195 (4.0)   | 1.22 (1.01–1.48)       |     |
| Gender              |               |             |                        |
| Male                | 31 (3.2)      | 31 (3.7)    | 1.00 (0.61–1.65)       | 0.47 |
| Female              | 332 (2.9)     | 275 (2.4)   | 1.22 (1.04–1.43)       |     |
| Dietary calcium     |               |             |                        |
| (mg day⁻¹)          |               |             |                        |
| < 400               | 55 (2.7)      | 47 (2.4)    | 1.12 (0.76–1.66)       | 0.67 |
| 400–600             | 72 (2.8)      | 70 (2.6)    | 1.06 (0.76–1.47)       |     |
| 600–800             | 69 (2.9)      | 44 (1.8)    | 1.59 (1.09–2.33)       |     |
| 800–1100            | 91 (3.1)      | 86 (3.1)    | 1.05 (0.78–1.41)       |     |
| ≥ 1100              | 76 (2.9)      | 59 (2.3)    | 1.31 (0.94–1.85)       |     |
| Dietary calcium     |               |             |                        |
| (mg day⁻¹)          |               |             |                        |
| < Median (737 mg day⁻¹) | 189 (3.0)   | 160 (2.6)   | 1.21 (0.98–1.49)       | 0.90 |
| > Median            | 174 (2.8)     | 146 (2.3)   | 1.18 (0.95–1.47)       |     |
| Smoking history     |               |             |                        |
| Never               | 123 (2.4)     | 112 (2.2)   | 1.13 (0.87–1.45)       | 0.34 |
| Previous            | 88 (2.3)      | 66 (1.8)    | 1.28 (0.93–1.76)       |     |
| Current             | 46 (3.8)      | 33 (2.9)    | 1.49 (0.78–2.86)       |     |
| Diabetes mellitus   |               |             |                        |
| Yes                 | 39 (4.6)      | 44 (5.3)    | 0.82 (0.53–1.27)       | 0.07 |
| No                  | 324 (2.8)     | 262 (2.3)   | 1.26 (1.07–1.48)       |     |
| History of hypertension |         |             |                        |
| Yes                 | 121 (3.8)     | 107 (3.3)   | 1.16 (0.89–1.50)       | 0.41 |
| No                  | 123 (1.9)     | 89 (1.4)    | 1.37 (1.04–1.80)       |     |

Abbreviations: CaD, calcium and vitamin D; CI, confidence interval; HR, hazard ratio.
Acknowledgements

This study was funded by the Health Research Council of New Zealand, GreenLane Research and Education Fund, Estate of Grace EM Kay—Orakau Heart Research Scholarship Trust and the Francis and Phyllis Thornell Shore Memorial Scholarship. The Women's Health Initiative: Clinical Trials (WHI-CT) is conducted and supported by the NHLBI in collaboration with the WHI Study Investigators.

Disclaimer

This manuscript was prepared using a limited-access data set obtained from the NHLBI and does not necessarily reflect the opinions or views of the WHI or the NHLBI.

References

1. Bolland MJ, Barber PA, Doughty RN, Mason B, Horne A, Ames R et al. Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial. BMJ 2008;336:262–266.
2. Bolland MJ, Avenell A, Baron JA, Grey A, MacLennan GS, Gamble GD et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. BMJ 2010;341:c3691.
3. Bolland MJ, Grey A, Avenell A, Gamble GD, Reid IR. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women’s Health Initiative limited access dataset and meta-analysis. BMJ 2011;342:d2040.
4. Reid IR, Bolland MJ, Avenell A, Grey A. Cardiovascular effects of calcium supplementation. Osteoporos Int 2011;22:1649–1658.
5. Hsia J, Heiss G, Ren H, Allison M, Dolan NC, Greenland P et al. Calcium/vitamin D supplementation and cardiovascular events. Circulation 2007;115:846–854.
6. Lewis JR, Calver J, Zhu K, Flicker L, Prince RL. Calcium supplementation and the risks of atherosclerotic vascular disease in older women: results of a 5-year RCT and a 4.5-year follow-up. J Bone Miner Res 2011;26:35–41.
7. Grant AM, Avenell A, Campbell MK, McDonald AM, MacLennan GS, McPherson GC et al. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomised placebo-controlled trial. Lancet 2005;365:1621–1629.
8. Reid IR, Mason B, Horne A, Ames R, Reid HE, Bava U et al. Randomized controlled trial of calcium in healthy older women. Am J Med 2006;119:777–785.
9. Baron JA, Beach M, Mandel JS, van Stolk RU, Haile RW, Sandler RS et al. Calcium supplements for the prevention of colorectal adenomas. Calcium Polyp Prevention Study Group. N Engl J Med 1999;340:101–107.
10. Lagakos SW. The challenge of subgroup analyses—reporting without distorting. N Engl J Med 2006;354:1667–1669.
11. Aissmann SF, Pocock SJ, Enos LE, Kasten LE. Subgroup analysis and other (mis)uses of baseline data in clinical trials. Lancet 2000;355:1064–1069.
12. Jackson RD, LaCroix AZ, Caiss M, Wallace RB, Robbins J, Lewis CE et al. Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med 2006;354:669–683.
13. Wang L, Manson JE, Song Y, Sesso HD. Systematic review: Vitamin D and calcium supplementation in prevention of cardiovascular events. Ann Intern Med 2010;152:315–323.