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RESEARCH ARTICLE

General obstetrics

Calcium supplementation for the prevention of pre-eclampsia: Challenging the evidence from meta-analyses

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Abstract

Objective: To investigate the validity of the conclusion from Cochrane reviews and meta-analyses that treatment with calcium supplementation during pregnancy reduces the risk for pre-eclampsia by 55%, which has been influential in international guidelines and future research.

Design: Sensitivity analysis of data from Cochrane reviews of trials evaluating high-dose calcium supplementation (of at least 1 g/day) for reduction of pre-eclampsia risk.

Setting: Systematic review and meta-analysis.

Population: The Cochrane reviews and meta-analyses included 13 trials enrolling a total of 15 730 women. Random-effects meta-analysis of these studies resulted in a mean risk ratio (RR, calcium/placebo) of 0.45 (95% confidence interval [CI] 0.31–0.65; $p < 0.0001$).

Methods: We carried out a sensitivity analysis of evidence from the relevant Cochrane review, to examine the impact of study size.

Main outcome measures: pre-eclampsia.

Results: In the three largest studies, accounting for 13 815 (88%) of total recruitment, mean RR was 0.92 (95% CI 0.80–1.06) and there was no evidence of heterogeneity between studies ($I^2 = 0$). With inclusion of the smaller studies, mean RR decreased to 0.45 and I^2 increased to 70%.

Conclusions: In assessment of the effect of calcium supplementation on pre-eclampsia risk, the naive focus on the mean of the random-effects meta-analysis in the presence of substantial heterogeneity is highly misleading.

KEYWORDS
calcium supplementation, Cochrane reviews, meta-analysis, pre-eclampsia

1 | INTRODUCTION

Over the last five decades, many studies have been conducted to assess the potential benefit of calcium supplementation (of at least 1 g/day) during pregnancy to reduce the risk of pre-eclampsia. A Cochrane review and meta-analysis in 2010 included 13 randomised trials deemed to be of good quality, on a combined total of 15 730 women.[1–14] The random-effects meta-analysis resulted in a mean risk ratio (RR) for the incidence of pre-eclampsia of 0.45 (95% confidence interval [CI] 0.31–0.65) and the effect was greatest for women with low baseline calcium intake (eight trials, 10 678 women: RR 0.36, 95% CI 0.20–0.65).[14] This review was influential on the guideline issued in 2011 by the World Health Organization (WHO), which recommends calcium supplementation during pregnancy in areas where dietary calcium intake is low.[15]

In subsequent updates of the Cochrane systematic review, in 2014 and 2018, the same results from the original 13 trials were presented with RR of 0.45 (95% CI 0.31–0.65; $I^2 = 70\%$) in the 2014 review, and 0.45 (95% CI 0.31–0.65; $I^2 = 70\%$; low-quality evidence) in the 2018 review. These reviews also included the caveat that the calcium supplementation-related reduction in risk of pre-eclampsia may be overestimated because of heterogeneity between studies and possible

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publication bias.[16,17] This was followed by a statement that the effect was clear for those with low calcium diets (eight trials, 10 678 women: average RR 0.36, 95% CI 0.20–0.65; $I^2 = 76\%$) but not those with adequate calcium diets, despite the fact that in the studies with low baseline calcium intake there was a high degree of heterogeneity ($I^2 = 76\%$). In 2018, WHO confirmed their 2011 guideline, without reservations.[15,18] Similarly, a calcium supplementation-related 55% reduction in the risk of pre-eclampsia has been cited unreservedly in the National Institute for Health and Care Research Health Technology Assessment Programme funded the Calcium Supplementation for Prevention of Pre-eclampsia in High-Risk Women: CaPE Trial, which is currently recruiting in UK National Health Service hospitals.[19]

We sought to investigate the validity of the conclusion from successive Cochrane reviews and meta-analyses by undertaking a sensitivity analysis evaluating the influence of the smaller studies.

2 | METHODS

2.1 | Study participants

This was a sensitivity analysis of data from Cochrane reviews of trials of high-dose calcium supplementation (of at least 1 g/day) on the risk for pre-eclampsia, in 13 trials of 15 730 women.[14,16,17]

2.2 | Statistical analysis

Starting with the largest study in the Cochrane review,[14] a cumulative meta-analysis[20] comprising a sequence of random-effects meta-analyses adding studies in decreasing order of the total number of participants was performed. The mean RR and I^2 statistic were plotted against the total sample size.

The analysis was undertaken using the R statistical software,[21] using the package meta.[22]

3 | RESULTS

Of the 13 trials included in the Cochrane review,[14] eight were carried out in countries with low calcium intake,[1,3,4,6,7,9–11] four in countries with adequate calcium intake[2,5,8,12] and one in which dietary calcium was not specified.[13] Figure 1 shows the random effects meta-analysis with studies ordered from largest to smallest study size.

Figure 2 shows the estimated mean RR and the proportions of total variation explained by heterogeneity between the 13 studies. Starting with the largest study, results were obtained by adding studies according to total sample size. The three largest studies accounted for 13 815 (87.8%) of the total of 15 730 women included in the full analysis.[1–3] For these three larger studies, there was no evidence of heterogeneity ($I^2 = 0$) and the estimated mean RR was 0.92 (95% CI 0.80–1.06).

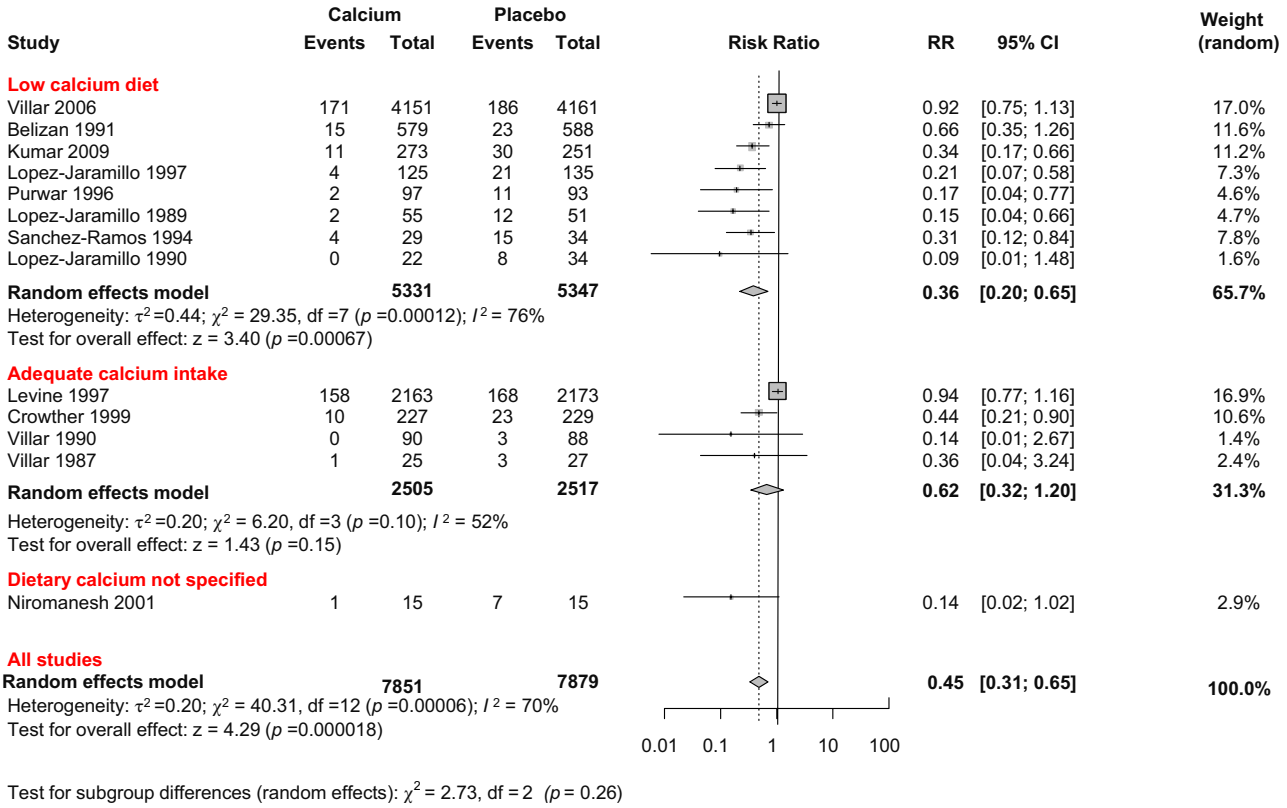

FIGURE 1 Risk ratio (RR) and 95% confidence interval (95% CI) for the effect of calcium supplementation versus placebo/no therapy on the incidence of preeclampsia in all 13 trials included in the Cochrane reviews. The studies are classified according to dietary calcium intake.

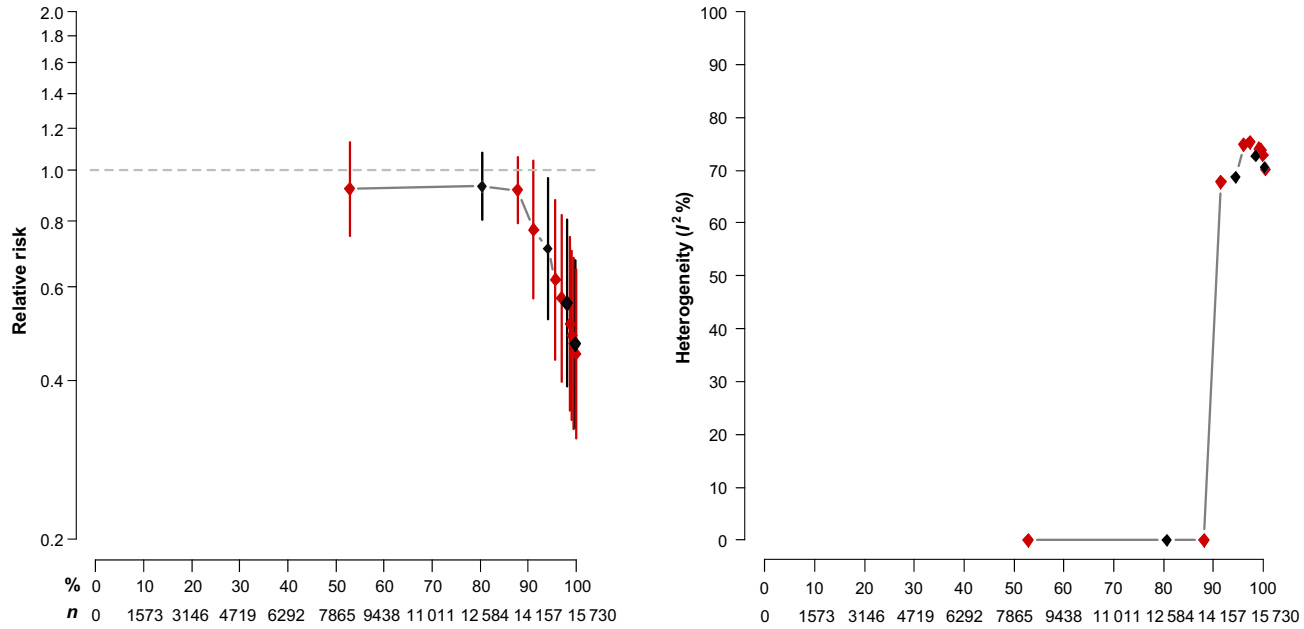

FIGURE 2 Results from meta-analyses with additional studies added according to sample size, largest to smallest. The left panel shows estimated mean risk ratios (calcium to placebo) with 95% confidence intervals by the total sample size *n* and %. The right panel shows the proportion of total variation explained by heterogeneity. Results obtained from the addition of studies in low calcium populations are shown in red and those from adequate calcium populations are shown in black.

The smaller studies ranged in size from 30 to 524 patients, with a median of 142. Together, they accounted for 12.2% of women in the final analysis. With inclusion of these smaller studies, there was a substantial decrease in the estimated mean RR to 0.45 (95% CI 0.31–0.65) and a high degree of heterogeneity ($I^2 = 70\%$).

In the largest trial from countries with low calcium intake, there were 8312 women, accounting for 77.8% of the total of 10 678 women in the eight trials in the Cochrane review from such countries; there was no significant benefit of calcium supplementation on pre-eclampsia occurrence (RR 0.92, 95% CI 0.75–1.13). The next largest study from the low calcium intake group included 1167 women and there was no heterogeneity between these two largest trials, which together accounted for 9479 (88.8%) of the total in the eight trials and again there was no significant benefit from calcium supplementation (Figure 2). With inclusion of the six smaller relevant studies, which together accounted for 11.2% of women included in the final analysis, there was a substantial decrease in estimated mean RR (0.36, 95% CI 0.20–0.65), and an increase in heterogeneity ($I^2 = 76\%$).

The latest Cochrane review contrasts low calcium diet trials and adequate calcium trials, saying that the effect is clear in the eight low calcium trials but not those with adequate calcium diets. However, Figure 3 shows the estimated mean RR and 95% CI obtained separately for trials with adequate and low calcium diets. Although the average effect was statistically significant in the low calcium intake trials and not in the adequate calcium intake trials, the impact of the smaller studies was similar in both the low calcium and the adequate calcium intake trials. The difference between low and adequate calcium intake studies is explained by the relatively larger number of smaller studies that enrolled participants with low calcium intake diets.

4 | DISCUSSION

4.1 | Main findings

The main finding of this analysis is that meta-analyses of calcium supplementation of at least 1 g/day for prevention of pre-eclampsia are misleading, as they focus on the mean RR from random-effects meta-analyses of studies with a high degree of heterogeneity. The three largest studies account for 88% of all data in the Cochrane reviews, with no evidence of between-trial heterogeneity and little or no beneficial effect of calcium supplementation on pre-eclampsia prevention.[1–3] After the inclusion of ten small studies, accounting for only 12% of the total population, there was a substantial reduction (by 55%) of the overall risk of pre-eclampsia, but this was accompanied by a high degree of heterogeneity between studies ($I^2 = 70\%$).[1–13]

The reviews make the point that the effect was clear for those with low calcium diets, but not for those with adequate calcium diets. It is not clear what led to this conclusion; however, it is notable that the effect is overwhelmingly significant in the low calcium diet trials ($p = 0.0007$) but not in the adequate calcium trials ($p = 0.15$). As explained in the Cochrane Handbook,[23] it is a mistake to compare within-subgroup inferences such as *p* values. If one subgroup analysis is statistically significant and another is

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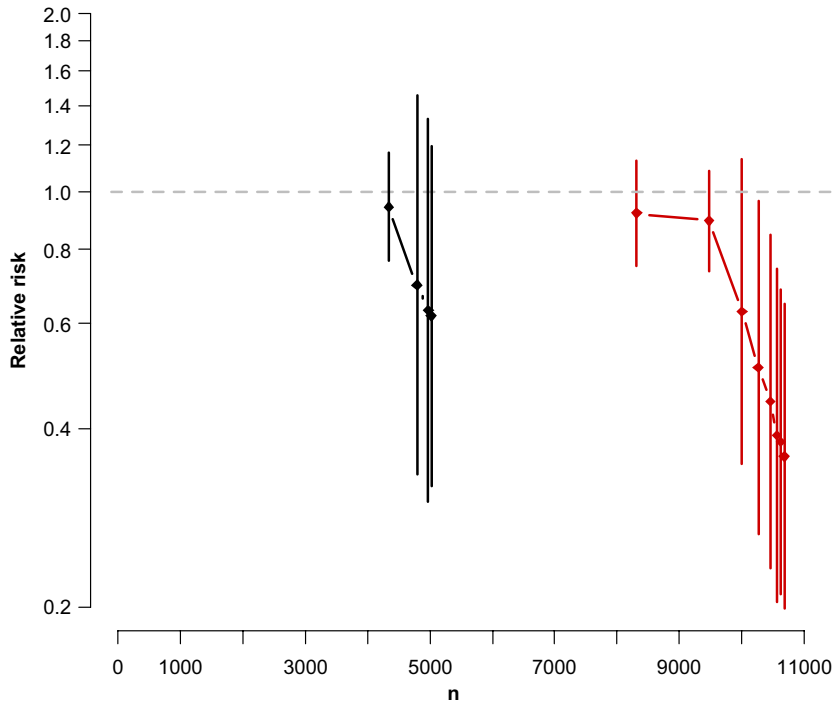

FIGURE 3 Results from meta-analyses with additional studies added according to sample size largest to smallest. Separate analyses were undertaken for those with adequate (black) and low calcium intake (red).

not, then the latter may simply reflect a lack of information rather than a smaller (or absent) effect. Our analysis (Figure 3) suggests that one explanation for the lack of significance for the adequate calcium studies is the smaller number of small trials.

In low calcium intake trials, two large studies account for 89% of all data, with no evidence of heterogeneity between them, and no beneficial effect demonstrated of calcium supplementation on pre-eclampsia occurrence. However, after inclusion of six small studies, accounting for only 11% of the total population, there was a substantial reduction (by 64%) of the overall risk for pre-eclampsia with substantial heterogeneity between studies ($I^2 = 76\%$).

The major impact of the smaller studies on the overall findings of the Cochrane reviews and meta-analyses is likely to be a reflection of publication bias, in which smaller studies showing substantial and statistically significant effects are published, whereas those showing little evidence of effectiveness are not. Other than publication bias, extreme effects could reflect a lack of trustworthiness[24]; more likely to occur in smaller trials with limited oversight and scrutiny. Instruments for assessment of trustworthiness such as the TRACT checklist[25] have been developed to address this problem.

4.2 | Strengths and limitations

The main strength of this analysis is the simple approach to demonstrating the impact of study size on the degree of heterogeneity between studies, in a way that is not apparent in funnel plots.

The conclusions of this study relate to the prevention of pre-eclampsia, defined as hypertension and new proteinuria in all relevant trials. However, the findings are not restricted to the impact of calcium supplementation on pre-eclampsia risk, but also relate to other interventions and outcomes in Cochrane reviews and any other meta-analyses.[14,16,17,26] It is likely that similar approaches of reporting mean RR from random-effects meta-analyses, despite high heterogeneity between studies in meta-analyses, are widespread.

4.3 | Interpretation of results and implications for clinical practice

The WHO guidelines for calcium supplementation are just one example of the proliferation of guidelines by professional societies and others, aimed at ensuring that the best preventive interventions or treatment options are provided to the appropriate patients at the appropriate time; these guidelines often rely on meta-analyses to support their recommendations. The limitations of meta-analysis in the presence of heterogeneity are well-recognised. In 1997, Eysenck stated that 'Effect sizes summed over heterogeneous data can hardly be accorded any validity – yet such data can be cited as proving the value of treatment'.[27] In 2008, Higgins et al.[28] explained that the naive presentation of inference only on the mean of the random-effects distribution is highly misleading and pointed out that particular caution

is warranted when interpreting any meta-analysis when a relationship exists between treatment effect and study size. The Cochrane Handbook emphasises the need to take into account any statistical heterogeneity when interpreting the results.[23]

Pitfalls arising from the indiscriminate reliance on mean effects from random effects meta-analyses are compounded by the traditional pyramid of evidence, which has systematic reviews and meta-analyses at the top. A large, well-conducted, multicentre trial testing the relevant hypothesis, provides higher-quality evidence than meta-analysis of all trials. Alternative, more nuanced ways of classifying evidence have been suggested, that take explicit account of between-trial heterogeneity in outcomes.[29]

5 | CONCLUSIONS

Guidelines and further research should exercise real caution when interpreting the mean effect size from random-effects meta-analyses, when there is between-trial heterogeneity in effect and an association between treatment effect and study size.

AUTHOR CONTRIBUTIONS

DW and KHN conceptualised and designed the study. DW wrote the first draft of the paper. All authors revised and contributed to the intellectual content of the manuscript.

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None.

CONFLICT OF INTEREST STATEMENT

None declared.

ETHICS APPROVAL

The study involved analysis of published data and no ethics approval was necessary.

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