

Role of multivitamins and mineral supplements in preventing infections in elderly people: systematic review and meta-analysis of randomised controlled trials

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Abstract

Objective To evaluate the effectiveness of multivitamins and mineral supplements in reducing infections in an elderly population.

Design Systematic review and meta-analysis of randomised controlled trials.

Data sources Medline and other databases. Reference lists of identified articles were inspected for further relevant articles.

Selection of studies Trials were included if they evaluated the effect of multivitamins and mineral supplements on infections in an elderly population.

Review methods Studies were assessed for the methodological quality by using the Jadad instrument. If the data required for the analyses were not available from the published articles we requested them from the original study authors. Meta-analysis was undertaken on three outcomes: the mean difference in number of days spent with infection, the odds ratio of at least one infection in the study period, and the incidence rate ratio for the difference in infection rates. Data on adverse events were also extracted.

Results Eight trials met our inclusion criteria. Because the outcomes reported were inconsistent, only a proportion of the trials could be included in each meta-analysis. Multivitamins and mineral supplements were found to reduce the mean annual number of days spent with infection (three studies) by 17.5 (95% confidence interval 11 to 24, $P < 0.001$). The odds ratio for at least one infection in the study period (three studies) was 1.10 (0.81 to 1.50, $P = 0.53$). The infection rate ratio (four studies) was 0.89 (0.78 to 1.03, $P = 0.11$). Reporting of adverse events was poor.

Conclusion The evidence for routine use of multivitamin and mineral supplements to reduce infections in elderly people is weak and conflicting. Study results are heterogeneous, and this is partially confounded by outcome measure.

Introduction

Ageing is associated with physiological and economical changes that compromise nutritional status, and also with an increased susceptibility to infections. Public interest in vitamin supplements is enormous: 20-30% of the population in developed countries cur-

rently use such supplements.¹ Few studies have documented their benefits, which has raised concern recently.^{1,2} In elderly people, supplementation with different nutrients improves immune status. Most of these studies looked at the effect of micronutrients on vaccine responses and other surrogate markers of immune response. The clinical importance of these findings is still a subject of debate; some believe that the micronutrients have a major role³ and others believe that they have only a minor role⁴ in reducing the frequency of infections in elderly people.

We undertook a systematic review and meta-analysis of randomised controlled trials evaluating the use of multivitamin and mineral supplements to prevent infections in an elderly population.

Methods

We searched computerised databases to identify relevant randomised controlled trials covering the period from 1966 to the first week of January 2004. We supplemented this search by examining published reviews, guidelines, and conference abstracts (for details of the specific search strategies used, see appendix 1 on bmj.com). We scrutinised the reference lists of identified relevant articles to identify any further studies.

Selection

Studies had to be randomised placebo controlled trials, evaluating a combination of multivitamins and mineral supplements in an elderly population. Studies also had to report an infection related outcome.

Data extraction and quality assessment

We focused our attention on the three most widely used and reported outcomes: the mean difference in number of days spent with infection, the odds ratio of at least one infection in the study period, and the incidence rate ratio for the difference in infection rates. Additionally, we extracted any data on adverse events. The authors extracted all outcome data relating to

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Search strategies are on bmj.com



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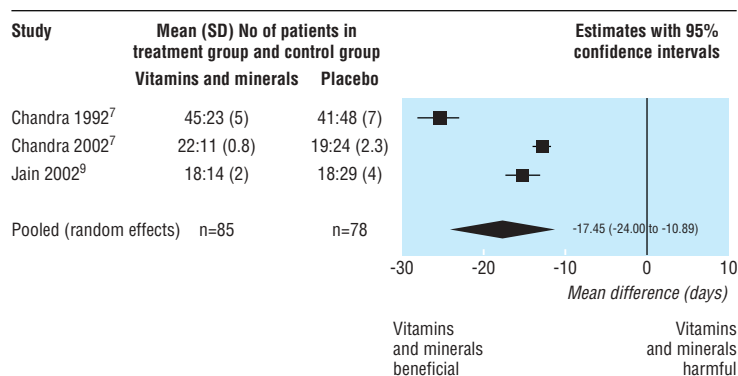


Fig 1 Random effects meta-analysis of outcome: mean difference in number of days of infection between multivitamin+supplement and placebo groups in 12 months

infections and disagreements were resolved by consensus. If data were not available from the published reports, we wrote requesting the information. We used the Jadad scoring system to assess the methodological quality.⁵

Quantitative data synthesis

We used random effects models to perform meta-analyses if the heterogeneity between studies was estimated to be greater than zero; otherwise we used the model reduced to a fixed effect model. The continuous outcome (the mean difference in number of days of infection over 12 months) was combined on the mean difference scale, the binary outcome (one or more infections during the study period) on the (log) odds ratio scale and the incidence rate (the rate of infections during the study period) using weighted (fixed effect) Poisson regression. The relatively small number of studies reporting each outcome precluded the use of funnel plots to assess the possibility of publication bias and meant that using meta-regression to assess heterogeneity between studies was also not possible.

Results

We screened a total of 1490 abstracts from the combined searches. This identified 36 potentially relevant studies, but on obtaining and reading the articles, only eight met the inclusion criteria (see bmj.com for details on design characteristics and quality assessment scores). Variability between studies is considerable with respect

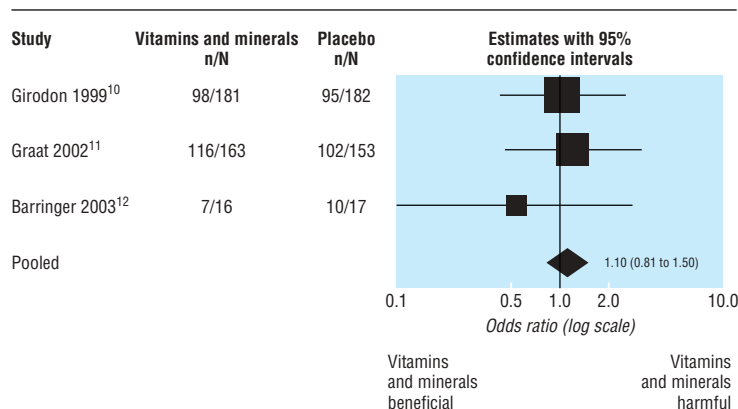


Fig 2 Fixed effects meta-analysis of outcome: odds ratio for at least one infection during the study period between multivitamin+supplement and placebo groups

to duration of follow-up, infections assessed, and number of subjects. Jadad scores were reasonable for all studies except one, but this probably, at least in part, reflects the brevity of the study report. Three of the trials used a 2x2 factorial trial, and only the two most relevant arms are included in this meta-analysis.

Meta-analysis of first outcome

Figure 1 shows that all three trials individually show a significant reduction in days of infection for the multivitamin and mineral group and the pooled estimate of a benefit of approximately 17.5 days (95% confidence interval 11 to 24) is highly significant (P<0.001). Although the direction of results is consistent, studies are heterogeneous (the I² statistic is estimated to be 97.3%, which is considered very large⁶). We had a concern that the reported standard deviations for this outcome seemed to be very small and may in fact be standard errors. Hence we performed an extreme sensitivity analysis in which we re-analysed the data under the assumption that this error had been made in all three trials; the pooled estimate remained similar and still significant (14 day benefit, 10 to 18, P<0.001).

Meta-analysis of second outcome

Figure 2 shows that the odds ratios for two of the three studies are greater than one, and the pooled odds ratio is 1.10 (0.81 to 1.50). Hence this meta-analysis provides little support for the benefit of multivitamin, and minerals; however, the wide confidence interval makes the findings inconclusive (P=0.53).

Meta-analysis of third outcome

Figure 3 shows that the pooled incidence risk ratio for the fixed effect model is 0.89 (0.78 to 1.03). Hence there is an indication that multivitamins and minerals may reduce the number of infections, but this does not reach conventional significance levels (P=0.11).

Reporting of adverse events

Reporting of adverse event outcomes for the trials was so incomplete that meta-analysis was not possible. One trial reported some dropouts (four in the treatment group and one in the placebo group) because of nausea, which in our interpretation could be attributable to the intervention. Two further trials indirectly implied that no adverse events causing dropout occurred. Two more trials stated clearly that there were no dropouts owing to the effects of the intervention. No mention of adverse events was given in the remaining three trials.

Discussion

The evidence for the effectiveness of the routine use of multivitamins in an elderly population to reduce infections is of poor to moderate quality, heterogeneous, and conflicting. We found little evidence of adverse events due to the intervention, but this may be due to poor reporting. It is worth noting that other studies using excessive micronutrient supplements (in larger doses than implemented in any of the trials reviewed here) have been shown to have toxic effects and may impair cellular function.¹⁵

The potential underlying mechanism by which multivitamins and minerals generally and specifically prevent infections is still uncertain; we do not know whether it is related to improvement in immunity, improvement of the underlying deficiency, or other reasons.

We have qualitatively considered potential factors that may influence the observed heterogeneity. The exact composition of multivitamin and mineral supplements may in part be responsible; two studies used dosages of nutrients that were close to recommended dietary allowances in France and the United States, three studies used nutrient dosages similar to the recommended dietary allowance in the United States, with the exception of vitamin E and β carotene, two studies used a daily oral tablet that contained amounts of vitamins and minerals similar to those found in most commercial multivitamin and mineral supplements, and one study used dosages at the level of recommended dietary allowances for vitamins and 25-50% of recommended dietary allowances for minerals.

A further potential explanation for heterogeneous results is variability in the baseline nutritional status of study participants. Differences were considerable in the baseline rates of infection in the control groups of the four trials reporting infection rates (fig 3). Further, two trials even had marked imbalances in nutrient deficiencies at baseline. The subject populations recruited differed between studies. Two trials recruited exclusively from nursing homes, and one trial included a much higher proportion of people with type 2 diabetes (39%) than any of the others. In the original trial report, a subgroup analysis by diabetes status was carried out, and nearly all the intervention effect was found to be attributed to the diabetic patients. The most beneficial effect sizes were observed in small studies, which may mean this literature is subject to publication bias. Loss to follow-up in some trials was considerable, which could induce bias in those studies. Other factors that may influence outcome include the length of study follow-up and the seasonal changes it covered, which infections were being investigated and how they were measured, and the quality of the studies.

Limitations of the study

We identified only a modest number of relevant studies. This limited the assessments of publication bias

What is already known on this topic

Ageing is associated with an increased susceptibility to infection

Currently, interest is great in the use of multivitamins and mineral supplements, with the hope of preventing infections

What this study adds

The evidence for routine use of multivitamin and mineral supplements to reduce infections in the elderly is weak and conflicting

Therefore the evidence does not support a policy recommending the routine use of such supplements in all elderly people

Further randomised controlled trials using consistent outcome measures are needed before routine use can be recommended

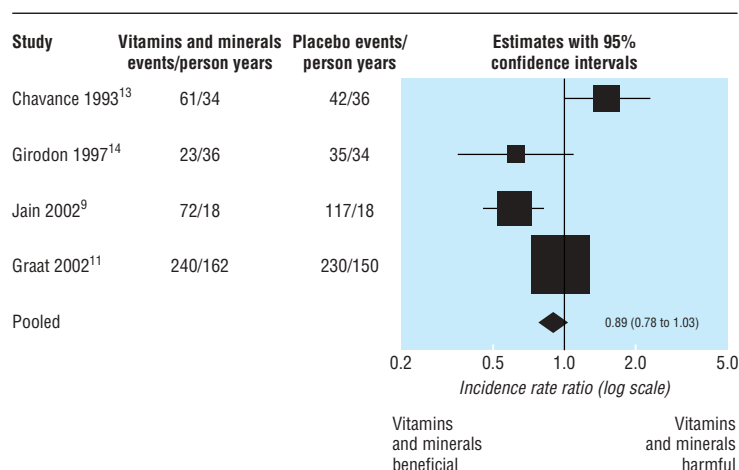


Fig 3 Fixed effects meta-analysis of outcome: incidence rate ratio for infection between multivitamin+supplement and placebo groups

and the formal exploration of the considerable heterogeneity between studies. Considerable variability existed in the outcome definitions used to report infections. However, it is noteworthy that in the two instances when two outcomes were reported by a single trial, they gave similar results, implying, perhaps, that definition of outcome is not the most important source of variation. Disappointingly, no more than four studies reported any one outcome.

Comparison with previous studies

Although one previous paper has reviewed the role of micronutrients in preventing infections in elderly people,¹⁶ to the best of our knowledge no previous systematic review or meta-analysis of the use of micronutrients in preventing infections in elderly people has ever been undertaken.

Implications for practice

Currently, not enough evidence exists to recommend the routine use of micronutrient supplements for an elderly population. However, the results of this review are sufficiently encouraging to warrant further and more expansive studies.

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Quetiapine and rivastigmine and cognitive decline in Alzheimer's disease: randomised double blind placebo controlled trial

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Abstract

Objectives To determine the respective efficacy of quetiapine and rivastigmine for agitation in people with dementia in institutional care and to evaluate these treatments with respect to change in cognitive performance.

Design Randomised double blind (clinician, patient, outcomes assessor) placebo controlled trial.

Setting Care facilities in the north east of England.

Participants 93 patients with Alzheimer's disease, dementia, and clinically significant agitation.

Intervention Atypical antipsychotic (quetiapine), cholinesterase inhibitor (rivastigmine), or placebo (double dummy).

Main outcome measures Agitation (Cohen-Mansfield agitation inventory) and cognition (severe impairment battery) at baseline and at six weeks and 26 weeks. The primary outcome was agitation inventory at six weeks.

Results 31 patients were randomised to each group, and 80 (86%) started treatment (25 rivastigmine, 26 quetiapine, 29 placebo), of whom 71 (89%) tolerated the maximum protocol dose (22 rivastigmine, 23 quetiapine, 26 placebo). Compared with placebo, neither group showed significant differences in improvement on the agitation inventory either at six weeks or 26 weeks. Fifty six patients scored > 10 on the severe impairment battery at baseline, 46 (82%) of whom were included in the analysis at six week follow up (14 rivastigmine, 14 quetiapine, 18 placebo). For quetiapine the change in severe impairment battery score from baseline was estimated as an average of -14.6 points (95% confidence interval -25.3 to -4.0) lower (that is, worse) than in the placebo group at six weeks ($P=0.009$) and -15.4 points (-27.0 to -3.8) lower at 26 weeks ($P=0.01$). The corresponding changes with rivastigmine were -3.5 points (-13.1 to

6.2) lower at six weeks ($P=0.5$) and -7.5 points (-21.0 to 6.0) lower at 26 weeks ($P=0.3$).

Conclusions Neither quetiapine nor rivastigmine is effective in the treatment of agitation in people with dementia in institutional care. Compared with placebo, quetiapine is associated with significantly greater cognitive decline.

Introduction

Antipsychotic drugs are commonly prescribed to many people with dementia (up to 45%) in residential or nursing homes,¹ often for prolonged periods. Antipsychotics have modest efficacy² but are commonly associated with substantial adverse effects and, more seriously, an increased risk of stroke has been reported with the atypical antipsychotics, risperidone and olanzapine.³ There are no published randomised controlled trials for other atypical antipsychotics in people with dementia, although a published abstract indicates some benefit of quetiapine in those with agitation,⁴ and preliminary evidence indicates that cholinesterase inhibitors may also improve agitation.⁵

One observational study reported a doubling in the rate of cognitive decline in patients with dementia taking typical antipsychotics,⁶ although the impact on cognition of newer atypical antipsychotics, was not determined.

We compared quetiapine and rivastigmine with placebo in patients with dementia and agitation in nursing homes in a randomised double blind placebo controlled trial over 26 weeks. Our primary objective was to determine whether either drug was better than placebo for agitation. We also evaluated whether there was a significant difference between the individual



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