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

Alia El-Kadiki, Alexander J Sutton

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. Owing to inconsistency in the outcomes reported, 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 = 0.55). 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

Elderly people constitute the fastest growing population segment of societies in the developed world. They are vulnerable to infections, which are very common in older people. Moreover, elderly people are two to 10 times more likely to die of a variety of infections than are young adults. Public interest in vitamin supplements is enormous: 20-30% of people worldwide take multivitamin and mineral supplements, hoping to promote health, but few studies have documented their benefits, which has raised concern in the literature recently. It has been shown that 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 role and others believe that they have only a minor role 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. We focus on studies that evaluate multivitamin and mineral supplements and exclude those that investigate single vitamins or minerals since multivitamin supplements are more widely used.

Methods

We searched computerised publication databases to identify relevant randomised controlled trials (AMED, Biological Abstracts, British Nursing Index, CINAHL, Citation Indexes, Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), EBM Reviews, Embase, International Bibliographic Information on Dietary Supplements (IBIDS), Medline, NHS Centre for Reviews and Dissemination databases, and PreMedline). The searches covered the period from 1966 to the first week of January 2004. We supplemented this search by examining published reviews, guidelines, Health Evidence Bulletin Wales, 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 missed by the previous searches.

Selection

In order to be included in the review, a study had to be a randomised placebo controlled trial, 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**

After an initial scoping exercise on the included trial reports, we decided to focus 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 infections and where disagreements existed they reached consensus through discussion. If data required for the planned analyses were not available from the published reports, we wrote to the corresponding authors of the primary studies and requested the necessary information. We used the Jadad scoring system to assess the methodological quality of the individual randomised controlled trials.

**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. We used weighted Poisson regression to combine the continuous outcome (the mean difference in number of days of infection over 12 months) 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).

Although we intended to use funnel plots to assess the possibility of publication bias, the relatively small number of studies reporting each outcome precluded such an assessment. Similarly, we had planned to use meta-regression to assess heterogeneity between studies, but this was not possible because of the limited data available. We undertook this review and reported it in accordance with the guidelines set out in the QUOROM statement.

**Results**

Figure 1 outlines the results of the trial selection process. 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. This identified 36 potentially relevant studies, but on obtaining and reading the articles, only eight met the inclusion criteria. We undertook this review and reported it in accordance with the guidelines set out in the QUOROM statement.

**Meta-analysis of second outcome**

Three trials reported at least one infection during the study period for vitamins and minerals compared with placebo. As figure 3 indicates, the odds ratios for two of the three studies included are greater than one, and the pooled odds ratio is 1.10 (0.81 to 1.50) (this is a fixed effect analysis as the between study heterogeneity was estimated as zero). 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**

Four trials reported the incidence rate ratio of infection for vitamins and minerals compared with placebo. The pooled incident risk ratio for the fixed effect model is 0.89 (0.78 to 1.03; fig 4). 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. We summarise the data that could be extracted. One trial reported some drop-outs (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 (by citing the presence of adverse events in other studies using higher doses). Two more trials stated clearly that there were no drop-
outs owing to the effects of the intervention.25 26 No mention of adverse events was given in the remaining three trials.22 23 27

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 recommended)28 have found in most commercial multivitamin and mineral supplements, and these differences in composition may in part be responsible. Two studies used dosages of nutrients that were close to recommended dietary allowances in France and the United States, with the exception of vitamin E and one study used dosages at the level of recommended daily allowances in the United Kingdom. Three studies used nutrient dosages similar to the recommended dietary allowance in the United States, with the exception of vitamin E and one study used dosages at the level of recommended dietary allowances for vitamins and 25-50% of recommended dietary allowances for minerals.29 Table 2 shows a comparison with recommended daily allowances in the United Kingdom.

A further potential explanation for heterogeneous results is variability in the baseline nutritional status of study participants. Differences were certainly considerable in the baseline rates of infection in the control groups of the four trials reporting infection rates (fig 4). Further, two trials22 23 even had marked imbalances in nutrient deficiencies at baseline. The subject populations recruited differed between studies (table 1, final col-

Table 1 Characteristics of the trials included in the meta-analyses

<table>
<thead>
<tr>
<th>Study (location)</th>
<th>Age of trial participants in years</th>
<th>Duration of follow-up</th>
<th>Infections assessed</th>
<th>No of subjects in placebo group</th>
<th>No of subjects in treatment group</th>
<th>Jadad score</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chavance et al 1993 (France)27</td>
<td>60+</td>
<td>4 months</td>
<td>Respiratory, nose, throat, ear, skin, mouth, urinary, and gynaecological infections</td>
<td>108 (of which 7 were lost to follow-up, leaving an effective sample size of 101)</td>
<td>110 (of which 7 were lost to follow-up, leaving an effective sample size of 103)</td>
<td>3</td>
<td>Double blind</td>
</tr>
<tr>
<td>Girardon et al 1999 (France)27</td>
<td>65+</td>
<td>2 years (maximum)</td>
<td>Respiratory and symptomatic urogenital infections</td>
<td>162 (of which 4 withdrew and 51 died during the study, but all were included in analysis)</td>
<td>181 (of which 3 withdrew and 55 died during the study, but all were included in analysis)</td>
<td>4</td>
<td>A double blind, 2×2 factorial trial (arms multivitamin only and minerals only excluded from meta-analyses) Population was from nursing homes</td>
</tr>
<tr>
<td>Chandra 1992 (United States)24</td>
<td>65+</td>
<td>12 months</td>
<td>Any infection (diagnosis was based on clinical features and laboratory tests included blood count, radiography of the chest and sinuses, bacterial and fungal cultures of sputum, urine and blood, C reactive protein, and erythrocyte sedimentation rate)</td>
<td>48</td>
<td>48</td>
<td>4</td>
<td>Double blind</td>
</tr>
<tr>
<td>Barringer et al 2003 (United States)24</td>
<td>65+</td>
<td>12 months</td>
<td>Upper respiratory tract infection, lower respiratory tract infection, influenza-like syndrome, gastrointestinal infection, and urinary tract infection</td>
<td>17</td>
<td>18 65 (2 dropped out and were lost to follow-up leaving an effective sample size of 16)</td>
<td>4</td>
<td>People aged &gt;65 years were excluded from the analysis. A large proportion of subjects had diabetes. Double blind</td>
</tr>
<tr>
<td>Snell et al 2002 (Netherlands)28</td>
<td>60+</td>
<td>15 months (maximum)</td>
<td>Acute respiratory tract infections</td>
<td>230</td>
<td>240</td>
<td>3</td>
<td>Double blind, 2×2 factorial trial. Arms of vitamin E only and multivitamin-mineral + vitamin E have been excluded from meta-analyses</td>
</tr>
<tr>
<td>Chandra 2002 (location not specified)23</td>
<td>50-65</td>
<td>12 months</td>
<td>Common adult infection illnesses diagnosed by fever, cough, elevated erythrocyte sedimentation rate and C reactive protein, x ray of the sinuses and chest, blood culture, sputum culture, and urine culture</td>
<td>22 (three lost to follow-up, leaving an effective sample size of 19)</td>
<td>22</td>
<td>4</td>
<td>Double blind</td>
</tr>
<tr>
<td>Jain 2002 (India)27</td>
<td>51-78</td>
<td>12 months</td>
<td>Respiratory infections</td>
<td>18</td>
<td>18</td>
<td>2</td>
<td>Blinding unclear</td>
</tr>
<tr>
<td>Girardon et al 1997 (France)27</td>
<td>65+</td>
<td>2 years</td>
<td>Respiratory and symptomatic urogenital infections</td>
<td>20 (of which 7 dropped out before end but were included in analysis)</td>
<td>21 (of which 7 dropped out before end but were included in analysis)</td>
<td>4</td>
<td>A double blind, 2×2 factorial trial (arms multivitamin only and minerals only excluded from meta-analysis) Population was from nursing homes</td>
</tr>
</tbody>
</table>
For example, 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 that trial, subjects younger than 65 were also recruited, but we excluded those from our analysis. 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 (relative risk for people with type 2 diabetes 0.18 (0.07 to 0.44), and for people without diabetes 0.98 (0.68 to 1.41)). A further observation is that the most beneficial effect sizes were observed in small studies, which may mean this literature is subject to publication bias. As noted in table 1, 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 and the formal exploration of the considerable heterogeneity between studies. A further limitation was that considerable variability existed in the outcome definitions used to report infections (table 3). 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 perhaps, that definition of outcome is not the most important source of variation. Disappointingly, no more than four studies.

Comparison with previous studies
Although one previous paper has reviewed the role of micronutrients in preventing infections in elderly people, 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 research
Large heterogeneity between the results of the different studies was observed. One reason for the relatively small number of trials included in this review was the subject of publication bias.
als included in this review is that many previous studies examined only immunological markers (which may or may not translate to similar effects in clinical outcomes). Therefore, future studies should look at the clinical end points (infections, preferably using a common outcome definition). A further source of design variability between existing studies is the composition of the supplements used. Therefore, a multi-arm trial comparing different doses of micronutrients may be appropriate to establish decisively whether they are effective, and if so, whether some doses are superior to others. Additionally, the target populations for future trials should be thought about carefully as results show that the intervention effect is potentially not constant across populations (nutritional status, frailty, type 2 diabetes status, etc).

Finally, it seems sensible to have a minimum follow up period of 12 months to provide full exposure to seasonal changes. Such a randomised controlled trial would provide valuable further evidence, allowing a subsequent update of this meta-analysis. Further, if future studies proved the intervention to be effective an economic evaluation of such a policy would need to be done, because of the cost implications of the widespread uptake of supplements.

**Fig 2** Random effects meta-analysis of outcome: mean difference in number of days of infection between multivitamin+supplement and placebo groups in 12 months

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean (SD) No of patients in treatment group and control group</th>
<th>Estimates with 95% confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chandra 1992</td>
<td>45:23 (5)</td>
<td>-17.45 (-24.00 to -10.89)</td>
</tr>
<tr>
<td>Chandra 2002</td>
<td>22:11 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Jain 2002</td>
<td>18:14 (2)</td>
<td></td>
</tr>
<tr>
<td>Pooled (random effects)</td>
<td>n=85</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vitamins and minerals harmful</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vitamins and minerals beneficial</td>
<td></td>
</tr>
</tbody>
</table>

**Fig 3** Fixed effect meta-analysis of outcome: odds ratio for at least one infection during the study period between multivitamin+supplement and placebo groups

<table>
<thead>
<tr>
<th>Study</th>
<th>Vitamins and minerals n/N</th>
<th>Placebo n/N</th>
<th>Estimates with 95% confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Girdon 1999</td>
<td>98/181</td>
<td>95/182</td>
<td></td>
</tr>
<tr>
<td>Graat 2002</td>
<td>116/163</td>
<td>102/153</td>
<td></td>
</tr>
<tr>
<td>Barringer 2003</td>
<td>7/16</td>
<td>10/17</td>
<td></td>
</tr>
<tr>
<td>Pooled</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vitamins and minerals harmful</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vitamins and minerals beneficial</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Fig 4** Fixed effect meta-analysis of outcome: incidence rate ratio for infection between multivitamin+supplement and placebo groups

<table>
<thead>
<tr>
<th>Study</th>
<th>Vitamins and minerals events/person years</th>
<th>Placebo events/person years</th>
<th>Estimates with 95% confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chavance 1993</td>
<td>61/34</td>
<td>42/36</td>
<td></td>
</tr>
<tr>
<td>Girdon 1997</td>
<td>23/36</td>
<td>35/34</td>
<td></td>
</tr>
<tr>
<td>Jain 2002</td>
<td>72/18</td>
<td>117/150</td>
<td></td>
</tr>
<tr>
<td>Graat 2002</td>
<td>240/162</td>
<td>230/150</td>
<td></td>
</tr>
<tr>
<td>Pooled</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vitamins and minerals harmful</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vitamins and minerals beneficial</td>
<td></td>
<td></td>
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</tbody>
</table>
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 in this area of considerable public health importance.

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Ethical approval: Not required.

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35 Goodwin JS, Garry PJ. Relationship between megadose vitamin supplementation and clinical trials. Lancet 1993;118:34.
37 Goodwin JS, Garry PJ. Relationship between megadose vitamin supplementation and clinical trials. Lancet 1993;118:34.