

Papers

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. 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, $P = 0.53$). 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

Elderly people constitute the fastest growing population segment of societies in the developed world.¹ In the United Kingdom the number of people older than 85 will continue to double every 30 years (1961: 300 000; 1991: 800 000; 2021: 1 500 000).² Ageing is associated with physiological and economical changes that compromise nutritional status.³ In addition, ageing has long been associated with an increased susceptibility 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.⁴

Public interest in vitamin supplements is enormous: 20-30% of the population in developed countries currently use such supplements.⁵ Millions 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.⁵⁻⁶ 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.⁷⁻¹⁶ The clinical importance of these findings is still a subject of debate; some believe that the micronutrients have a major role¹⁷ and others believe that they have only a minor role¹⁸ 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 (Science and Social Sciences), 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



Search strategies are on bmj.com

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.¹⁹

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.²⁰ We used Stata, version 8.2 (StataCorp, College Station, TX: StataCorp LP, 2003) for all statistical analyses.

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.^{21–28} All eight trials were placebo controlled. Table 1 provides details on design characteristics and quality assessment scores for the included studies. Variability between studies is considerable with respect to duration of follow-up, infections assessed, and number of subjects. Jadad scores were reasonable for all studies except one,²⁷ but this probably, at least in part, reflects the brevity of the study report. Table 1 also notes that three of the trials^{28 25 22} used a 2×2 factorial trial, and only the two most relevant arms are included in this meta-analysis. Table 2 gives the exact formulation of the multivitamin and mineral interventions given in each trial and indicates where differences between trials exist (these differences are considered further in the discussion).

As indicated in the methods, the outcome measures reported across the trials were not standardised. Table 3 provides a matrix indicating which trials reported which outcomes and could therefore be included in each meta-analysis.

Meta-analysis of first outcome

Three trials^{23 26 27} reported mean difference of number of days spent with infections on multivitamins and minerals compared

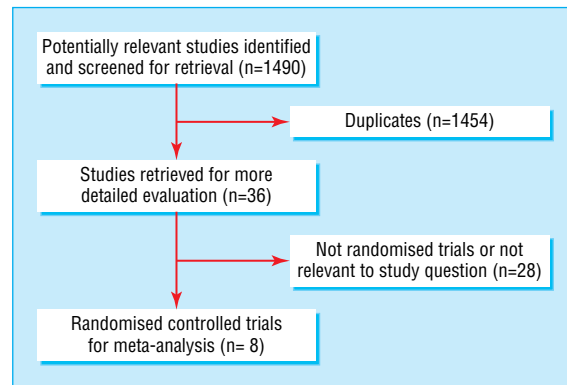


Fig 1 Results of literature search and selection of randomised controlled trials for the meta-analyses. Values are numbers of trials (QUOROM statement flow diagram)

with placebo over 12 months. Data are provided in figure 2, indicating 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 I^2 statistic, which indicates the proportion of variability in the weighted mean differences attributable to heterogeneity, is estimated to be 97.3%, which is considered (very) large).²⁹ 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 (by inflating the reported values by multiplying them by the number of subjects minus 1) 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

Three trials^{22 24 25} 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^{21 25 27 28} 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 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.²⁴ 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).^{22 28} Two more trials stated clearly that there were no drop-

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

Study (location)	Age of trial participants in years	Duration of follow-up	Infections assessed	No of subjects in placebo group	No of subjects in treatment group	Jadad score	Comments
Chavance et al 1993 (France) ²¹	60+	4 months	Respiratory, nose, throat, ear, skin, mouth, urinary, and gynaecological infections	108 (of which 7 were lost to follow-up, leaving an effective sample size of 101)	110 (of which 7 were lost to follow-up, leaving an effective sample size of 103)	3	Double blind
Girodon et al 1999 (France) ²²	65+	2 years (maximum)	Respiratory and symptomatic urogenital infections	182 (of which 4 withdrew and 51 died during the study, but all were included in analysis)	181 (of which 3 withdrew and 55 died during the study, but all were included in analysis)	4	A double blind, 2x2 factorial trial (arms multivitamin only and minerals only excluded from meta-analyses) Population was from nursing homes
Chandra 1992 (United States) ²³	65+	12 months	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)	48	48	4	Double blind
Barringer et al 2003 (United States) ²⁴	65+	12 months	Upper respiratory tract infection, lower respiratory tract infection, influenza-like syndrome, gastrointestinal infection, and urinary tract infection	17	18 65 (2 dropped out and were lost to follow-up leaving an effective sample size of 16)	4	People aged <65 years were excluded from the analysis. A large proportion of subjects had diabetes. Double blind
Graat et al 2002, (Netherlands) ²⁵	60+	15 months (maximum)	Acute respiratory tract infections	230	240	3	A double blind, 2x2 factorial trial. Arms of vitamin E only and multivitamin+mineral + vitamin E have been excluded from meta-analyses
Chandra 2002 (location not specified) ²⁶	50-65	12 months	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	22 (three lost to follow-up, leaving an effective sample size of 19)	22	4	Double blind
Jain 2002 (India) ²⁷	51-78	12 months	Respiratory infections	18	18	2	Blinding unclear
Girodon et al 1997 (France) ²⁸	65+	2 years	Respiratory and symptomatic urogenital infections	20 (of which 7 dropped out before end but were included in analysis)	21 (of which 7 dropped out before end but were included in analysis)	4	A double blind, 2x2 factorial trial (arms multivitamin only and minerals only excluded from meta-analysis) Population was from nursing homes

outs owing to the effects of the intervention.^{25 26} No mention of adverse events was given in the remaining three trials.^{21 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 implemented in any of the trials reviewed here) have been shown to have toxic effects and may impair cellular function.³⁰

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.

Although formal meta-regression to explore potential reasons for the observed heterogeneity was not possible because of the small numbers of studies reporting each outcome, we qualitatively consider potential factors that may influence

outcome below. Table 2 gives details of the exact composition of 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.^{22 28} Three studies used nutrient dosages similar to the recommended dietary allowance in the United States, with the exception of vitamin E and β carotene.^{23 26 27} 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,^{21 24} and one study used dosages at the level of recommended dietary allowances for vitamins and 25-50% of recommended dietary allowances for minerals.²⁵ 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 trials^{23 24} even had marked imbalances in nutrient deficiencies at baseline. The subject populations recruited differed between studies (table 1, final col-

Table 2 Details of composition of multivitamin and mineral supplements given in each trial

Details	Daily intake of supplements
Study (location)	
Chavance et al 1993 (France) ²¹	Vitamins A (retinol 5000 IU), B1 (thiamine) 2.25 mg, B2 (riboflavin) 2.6 mg, B6 (pyridoxine) 3 mg, B12 (cyanocobalamin) 9 µg, C 90 mg, D2 400 IU, E 30 IU, nicotinamid 20 mg, biotin 45 µg, pantothenic acid 10 mg Calcium 162 mg, iron 27 mg, zinc 22.5 mg, folic acid 0.4 mg, phosphorus 125 mg, iodine 150 µg, magnesium 100 mg, copper 3 mg, manganese 7.5 mg, potassium 7.5 mg
Girodon et al 1999 (France) ²²	Vitamins A (β carotene 6 mg), C 120 mg, E 15 mg Zinc 20 mg, selenium 100 µg
Chandra 1992 (United States) ²³	Vitamins A (retinol 400 µg), B1 (thiamine) 2.2 mg, B2 (riboflavin) 1.5 mg, niacin 16 mg, B6 (pyridoxine) 3.0 mg, B12 4.0 µg, C 80 mg, D 4 µg, E 44 mg, Calcium 200 mg, iron 16 mg, zinc 14 mg, folate 400 µg, copper 1.4 mg, selenium 20 µg, iodine 0.2 mg, magnesium 100 mg.
Barringer et al 2003 (United States) ²⁴	Vitamin A 4000 IU (β carotene 1000 IU), B1 (thiamine) 4.5 mg, B2 (riboflavin) 3.4 mg, niacin 20 mg, B6 (pyridoxine) 6 mg, B12 (cyanocobalamin) 30 µg, C (ascorbic acid) 120 mg, D 400 IU, E 60 IU, K 20 µg, biotin 0.03 mg, pantothenic acid 15 mg Calcium 120 mg, iron 16 mg, folic acid 400 µg, zinc 22.5 mg, selenium 105 µg, magnesium 100 mg, copper 2 mg, iodine 150 µg, manganese 4 mg, chromium 180 µg
Graat et al 2002, (Netherlands) ²⁵	A capsule contained: Vitamins A (retinol 600 µg, β carotene 1.2 mg), B1 (thiamine) 1.4 mg, B2 (riboflavin) 1.6 mg, niacin 18 mg, B6 (pyridoxine) 2.0 mg, B12 (cyanocobalamin) 1 µg, biotin 150 µg, C 60 mg, E 10 mg, D (cholecalciferol) 5 µg, K 30 µg, pantothenic acid 6 mg Calcium 74 mg, iron 4.0 mg, folic acid 200 µg, zinc 10 mg, selenium 25 µg, magnesium 30 mg, copper 1.0 mg, iodine 100 µg, phosphorus 49 mg, manganese 1.0 mg, chromium 25 µg, molybdenum 25 µg, silicium 2 µg Each participant received 2 capsules per day
Chandra 2002 (location not specified) ²⁶	Vitamins A (retinol 400 µg), B1 (thiamine) 2.2 mg, B2 (riboflavin) 1.5 mg, niacin 16 mg, B6 (pyridoxine) 3.0 mg, B12 4.0 µg, C 80 mg, D 4.0 µg, E 44 mg Calcium 200 mg, iron 16 mg, zinc 14 mg, copper 1.4 mg, selenium 20 µg, iodine 200 µg, magnesium 100 mg, folate 400 µg
Jain 2002 (India) ²⁷	Vitamins A (retinol 400 µg), B1 (thiamine) 2.2 mg, B2 (riboflavin) 1.5 mg, niacin 16 mg, B6 (pyridoxine) 3.0 mg, B12 4.0 µg, E 44 mg Calcium 200 mg, iron 16 mg, zinc 14 mg, copper 1.4 mg, selenium 20 µg, iodine 200 µg, magnesium 100 mg, folate 400 µg
Girodon et al 1997 (France) ²⁸	Vitamins A (β carotene 6 mg), C 120 mg, E 15 mg Zinc 20 mg, selenium 100 µg
Recommended daily allowances in the United Kingdom	
Men ≥50 ^{31 32}	Vitamins A 700 µg, B1 (thiamine) 0.9 mg, B2 (riboflavin) 1.3 mg, niacin 16 mg, B6 (pyridoxine) 1.4 mg, B12 1.5 µg, C 40 mg, D 10 µg (after age 65), E 10 mg Calcium 700 mg, iron 8.7 mg, zinc 9.5 mg, selenium 75 µg, phosphorus 550 mg, magnesium 300 mg, copper 1.2 mg, iodine 140 µg
Women ≥50 ^{31 32}	Vitamins A 600 µg, B1 (thiamine) 0.8 mg, B2 (riboflavin) 1.1 mg, niacin 12 mg, B6 (pyridoxine) 1.2 mg, B12 1.5 µg, C 40 mg, D 10 µg (after age 65), E 10 mg Calcium 700 mg, iron 8.7 mg, zinc 7.0 mg, selenium 60 µg, phosphorus 550 mg, magnesium 270 mg, copper 1.2 mg, iodine 140 µg

um). For example, two trials recruited exclusively from nursing homes,^{22 28} and one trial²⁴ 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,²⁴ a subgroup analysis by diabetes status was carried out, and nearly

Table 3 Reporting of infections by different definition of outcome (binary)

Study (location)	Mean days of infection	At least one infection	Infection rate
Chavance et al 1993 (France) ²¹			X
Girodon et al 1999 (France) ²²		X	
Chandra 1992 (United States) ²³	X		
Barringer et al 2003 (United States) ²⁴		X	
Graat et al 2002, (Netherlands) ²⁵		X	X
Chandra 2002 (location not specified) ²⁶	X		
Jain 2002 (India) ²⁷	X		X
Girodon et al 1997 (France) ²⁸			X
Total instances reported	3	3	4

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 reported any one outcome. The potentially conflicting results of the three different outcome measures could potentially be attributed to the selection of the specific trials that report that outcome. In an attempt to obtain more compatible data, we contacted authors of six of the trials and requested further information and sent a reminder when no reply arrived after the first query. Unfortunately no additional data were supplied for any of the trials.

Comparison with previous studies

Although one previous paper has reviewed the role of micronutrients in preventing infections in elderly people,³³ 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 tri-

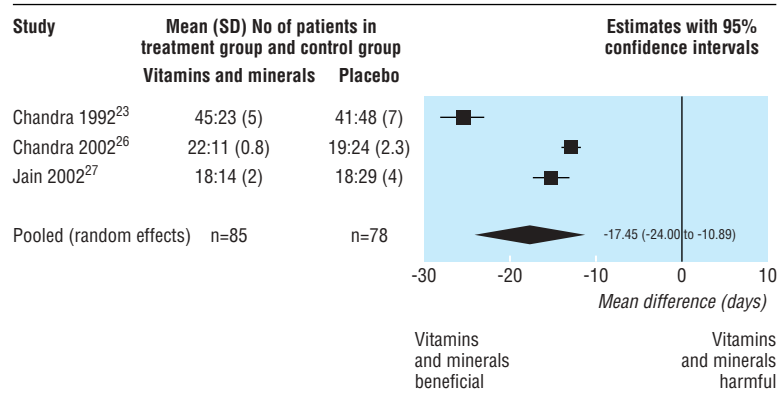


Fig 2 Random effects meta-analysis of outcome: mean difference in number of days of infection between multivitamin+supplement and placebo groups in 12 months

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.

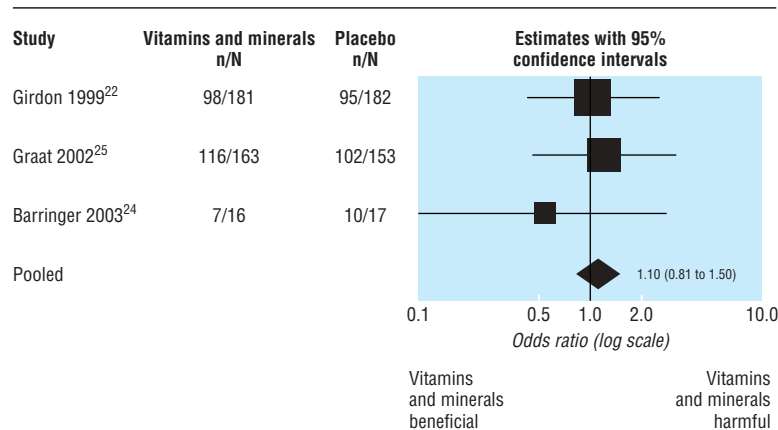


Fig 3 Fixed effect meta-analysis of outcome: odds ratio for at least one infection during the study period between multivitamin+supplement and placebo groups

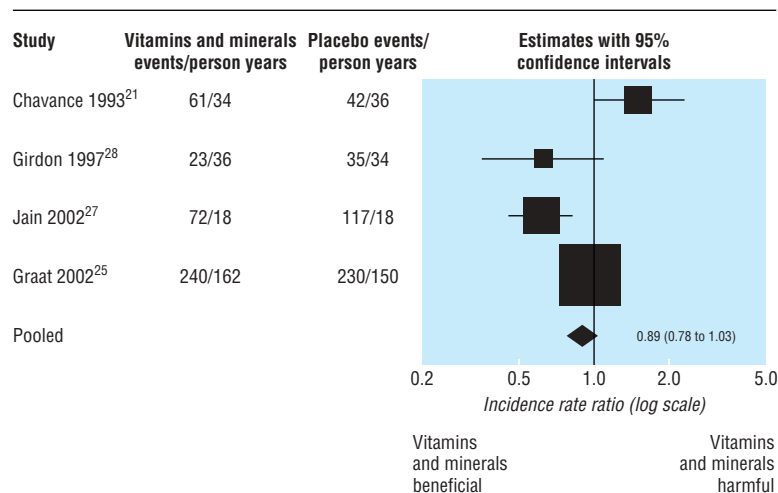


Fig 4 Fixed effect meta-analysis of outcome: incidence rate ratio for infection between multivitamin+supplement and placebo groups

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

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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