

Primary care

Effect of multivitamin and multimineral supplements on morbidity from infections in older people (MAVIS trial): pragmatic, randomised, double blind, placebo controlled trial

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Abstract

Objective To examine whether supplementation with multivitamins and multimineral influences self reported days of infection, use of health services, and quality of life in people aged 65 or over.

Design Randomised, placebo controlled trial, with blinding of participants, outcome assessors, and investigators.

Setting Communities associated with six general practices in Grampian, Scotland.

Participants 910 men and women aged 65 or over who did not take vitamins or minerals.

Interventions Daily multivitamin and multimineral supplementation or placebo for one year.

Main outcome measures Primary outcomes were contacts with primary care for infections, self reported days of infection, and quality of life. Secondary outcomes included antibiotic prescriptions, hospital admissions, adverse events, and compliance.

Results Supplementation did not significantly affect contacts with primary care and days of infection per person (incidence rate ratio 0.96, 95% confidence interval 0.78 to 1.19 and 1.07, 0.90 to 1.27). Quality of life was not affected by supplementation. No statistically significant findings were found for secondary outcomes or subgroups.

Conclusion Routine multivitamin and multimineral supplementation of older people living at home does not affect self reported infection related morbidity.

Trial registration ISRCTN: 66376460.

Introduction

At least 25% of older people in the United Kingdom take nutritional supplements.¹ Multivitamin and multimineral supplements are widely available and most brands have similar contents. Whether such supplementation influences infections in older people, particularly those not in nursing homes, is unclear from randomised controlled trials. A recent systematic review concluded that evidence for the routine use of

multivitamin and multimineral supplements in older people was weak and conflicting and that further randomised controlled trials were recommended.² That review included trials by Chandra,^{3 4} whose work has been questioned, leading one editor to retract a publication from one of the trials.^{3 5} An update to the review has been published.⁶

Supplementation is a low cost option for improving nutritional status. We undertook a pragmatic, randomised, placebo controlled trial to examine whether supplementation influences self reported infections, use of health services, and quality of life in people aged 65 or over.

Participants and methods

Participants were recruited from six general practices in Grampian, Scotland between February and December 2002. All people aged 65 or over who were registered with the practices were eligible, irrespective of chronic illness, unless their doctors considered them too unwell. Exclusion criteria were use of vitamin, mineral, or fish oil supplements in the previous three months (one month in the case of water soluble vitamins) or vitamin B₁₂ injection in the past three months.

Participants were recruited in their practice or at home. Detailed instructions were given about trial drugs, completion of daily diaries on infection and any contacts with primary care for infections, which were returned monthly, and the need to avoid vitamin or mineral supplements from other sources during the trial.

Interventions and outcomes

Participants were randomised to one tablet daily of a multivitamin and multimineral supplement (see bmj.com) or a matched sorbitol placebo. The supplement provided between 50-210% of UK



This is an abridged version; the full version is on bmj.com

reference nutrient intakes.⁷ Tablets were given to participants for one year.

Predefined primary outcomes were number of contacts with primary care (doctor and other primary care workers) for infection, number of self reported days of infection, and health related quality of life measured by the EuroQol and SF-12. Responses to the EuroQol were converted to a score using the EuroQol UK population tariff.⁸ We used prespecified procedures to code diaries for contacts with primary care for infection and days of infection.

Predefined secondary outcomes were number of antibiotic prescriptions in primary care, number of days that antibiotics were prescribed, number of hospital admissions, number of days in hospital with infection, number of infection related and all outpatient visits, adverse events reported by participants, and compliance with trial drugs. Hospital data were obtained from patient administration systems and hospital and general practice records.

General practice records were the only source of information on contacts with primary care and antibiotic prescriptions in over 94% of cases. Missing data were supplemented with participants' diary information when deaths subsequently occurred and the health board had removed the general practice notes, or when participants gave details of antibiotic prescriptions missing from the general practice records.

We carried out prespecified subgroup analyses for ages 65-74, 75-84, and ≥ 85 (the last two categories were later combined), sex, type of accommodation, and nutrition risk score (predictive of no deficiency versus one deficiency in any of four groups).

We used a nutrition assessment questionnaire for detecting older people at risk of nutritional deficiencies in vitamin C, vitamin D, folate, or iron.⁹ We developed questions from responses to a questionnaire and blood levels of nutritional status in a healthy local population of older people without evidence of infection.¹⁰

Randomisation and blinding

At recruitment, participants were randomly allocated to intervention or placebo by batch numbers generated by a password protected computer program. The program could be accessed by only the data programmer, blind to treatment allocation. The

identity of the tablets was concealed in a double envelope and kept locked in a cabinet during the trial. Randomisation was stratified by general practice and minimised by age, sex, and type of accommodation.

Assessors blind to trial allocation collected participant reported primary care and hospital data. Statisticians undertook analysis also blind to trial allocation.

Quality assurance

Two researchers independently entered a 10% random sample of diaries and questionnaires using a secure double data entry system. Agreement was 99%. We checked hospital records for all routinely collected data for everyone reporting a hospital admission or who had this documented in their general practice records. We entered a random sample of 10% of participants into the hospital's patient administration system to check whether any admissions had been missed; none were found.

Statistical analysis

Each comparison was by intention to treat, irrespective of compliance with pill taking. Statistical significance for all primary and secondary end points was based on two sided tests, with $2P \leq 0.05$; $2P \leq 0.01$ for subgroup analyses. For skewed continuous data, we calculated median and interquartile ranges. To account for skewness, we used negative binomial and poisson regression models to estimate the incidence rate ratio and 95% confidence intervals between groups, adjusting for the minimisation covariates.¹¹ We accounted for an excess number of zeroes in an outcome by using a zero inflated negative binomial or poisson model when appropriate.¹² A linear regression model was used to estimate the mean difference for health related quality of life measures between groups, after adjusting for baseline values and the minimisation covariates.¹³

Results

Overall, 910 of 10 090 people (9%) aged 65 or over were recruited (see [bmj.com](#)). Only 13% (n = 121) of participants were lost to follow-up or reported stopping taking tablets. The groups were well balanced at entry to the trial (see [bmj.com](#)).

On the basis of the questionnaire on nutrition, 32% of participants in the intervention group (n = 145) and

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Table 1 Contacts with primary care for infections and days of infection (including type) in community dwelling people aged 65 or older receiving multivitamin and multimineral supplementation or placebo for 12 months

Outcome measures	Supplement group		Placebo group		Incidence rate ratio (95% CI)
	No	Median (interquartile range) per person	No	Median (interquartile range) per person	
Contacts with primary care for infections*	879	1.0 (0-2)	930	1.0 (0-3)	0.96 (0.78 to 1.19); P=0.74
No in group	n=453	—	n=452	—	—
No of days of self reported infection†	8072	7.0 (0-24)	7871	8.0 (0-23)	1.07 (0.90 to 1.27); P=0.41
Upper respiratory tract infections	4068	1.0 (0-10)	3826	1.0 (0-10.25)	—
Lower respiratory tract infections	1782	0	1436	0	—
Genitourinary tract infections	690	0	579	0	—
Skin infections	1106	0	1256	0	—
Other infections	426	0	774	0	—
No in group	n=451	—	n=450	—	—

*Negative binomial model.

†Zero inflated negative binomial model.

Table 2 Data on prescriptions for antibiotics, hospital admissions, and infections in community dwelling people aged 65 or older receiving multivitamin and multiminer supplementation or placebo for 12 months

Outcome measure	Supplement group		Placebo group		Incidence rate ratio (95% CI)	P value
	No	Median (interquartile range) per person	No	Median (interquartile range) per person		
No of prescriptions for antibiotics in primary care*	619 (n=453)	1.0 (0.0-2.0)	641 (n=452)	0.0 (0.0-2.0)	0.98 (0.80 to 1.20)	0.85
Days of antibiotic prescribed per person in primary care*	(n=197)	10.0 (7.0-20.5)	(n=191)	10.0 (7.0-21.0)	0.93 (0.78 to 1.12)	0.45
No of hospital admissions	150 (n=453)	0 (0)	125 (n=452)	0 (0)	1.22 (0.89 to 1.67)	0.21
No of admissions for treatment of infections†	22 (n=453)	0 (0)	23 (n=452)	0 (0)	0.97 (0.54 to 1.74)	0.92
Days of hospital stay for treatment of infections*	(n=15)	9.0 (4.0-16.0)	(n=16)	13.5 (6.25-34.5)	0.74 (0.40 to 1.37)	0.34
No of outpatient appointments for treatment of infections‡	34 (n=453)	0 (0)	41 (n=452)	0 (0)	0.80 (0.38 to 1.67)	0.56
No of outpatient appointments§	999 (n=440)	1.0 (0.0-3.0)	845 (n=435)	1.0 (0.0-3.0)	1.16 (0.92 to 1.47)	0.22
No of deaths¶	8 (n=456)		4 (n=454)		—	0.25
No of adverse events‡	28 (n=456)	0 (0)	37 (n=454)	0 (0)	0.64 (0.22 to 1.93)	0.43

*Negative binomial model.

†Poisson model.

‡Zero inflated poisson model.

§Zero inflated negative binomial model.

¶Pearson's $\chi^2=1.333$.**Table 3** Subgroup analysis of contact with primary care for infection and days of infection by nutrition risk of community dwelling people aged 65 or older receiving multivitamin and multiminer supplementation for 12 months

Subgroup	Supplement group		Placebo group		Incidence rate ratio at risk versus not at risk (99% CI)†	P value
	Low risk	High risk	Low risk	High risk		
No of contacts with primary care staff for infections*:						
No at risk	309/453	144/453	336/452	116/452	—	—
Median (interquartile range) per person	1.0 (0.0-2.0)	1.0 (0.0-3.0)	1.0 (0.0-2.0)	1.0 (0.0-4.0)	1.16 (0.64 to 2.12)	0.52
No of infection days per person‡:						
No at risk	307/451	144/451	334/450	116/450	—	—
Median (interquartile range) per person	7.0 (0.0-20.0)	7.5 (0.0-32.5)	7.0 (0.0-22.0)	13.0 (0.0-32.0)	1.04 (0.64 to 1.69)	0.84

High risk—at risk for one or more of following nutrient deficiencies: vitamin C, vitamin D, folate, or iron; low risk—not at risk for vitamin C, vitamin D, folate, or iron deficiency.

*Negative binomial model.

†Estimated from a treatment by nutrition risk interaction term.

‡Zero inflated negative binomial model.

26% in the placebo group (n = 117) were at high risk of nutritional deficiency for iron, folate, vitamin C, or vitamin D. Slightly more people in the intervention group than in the placebo group were at high risk of iron deficiency (16% versus 8%).

We found no differences between the groups for compliance with drug taking (see [bmj.com](#)). Compliance in participants still taking tablets and returning information in diaries was over 91% throughout the trial. Compliance for all participants who had not died was over 78% throughout the trial.

We found no statistically significant effect from supplementation on our primary outcomes of contacts with primary care staff (mostly general practitioners and practice nurses) and days of infection per person: incidence rate ratio 0.96, 95% confidence interval 0.78 to 1.19 and 1.07, 0.90 to 1.27; table 1). Supplementation did not seem to affect quality of life (see [bmj.com](#)).

None of the secondary outcomes significantly differed between the groups (see [bmj.com](#)). We also found no important differences for subgroups on the basis of the nutrition risk score (table 3).

Purported adverse events were not serious and events did not significantly differ between the groups

(table 2). Similar numbers of participants in the groups died during the study (table 2).

Discussion

Regular use of commonly available multivitamin and multiminer supplements by community dwelling older people who do not already take supplements is unlikely to reduce the number of self reported infections or associated use of health services.

Our population had few people aged 85 or older or in nursing homes, who may be at higher risk of nutritional deficiency.¹ Our population may have been healthier than people who did not volunteer for the study. We did not, however, recruit people already taking nutritional supplements. By leaving out such people, we probably excluded those with healthier diets.¹ By using a simple questionnaire, we found that over 25% of the population was judged to be at high risk of nutritional deficiency and potentially more likely to benefit from supplementation, although this was not supported by our subgroup analyses. The proportion of the trial population at high risk of nutritional deficiency was similar to that in a

What is already known on this topic

The vitamin and mineral status of older people may be suboptimal, influencing immunity and risk of infection

It is unclear from previous trials in community dwelling older people whether multivitamin and multimineral supplements influence infection

What this study adds

Routine multivitamin and multimineral supplementation of older people living at home is unlikely to affect self reported infection related morbidity

Other members of the MAVIS trial were Kathryn Brownie (research assistant), Janice Cruden (trial secretary), Gladys McPherson (senior information technology manager), Clare Robertson (research assistant), and Joanne Warner (research assistant). We thank the participants, the staff of the general practices and medical records at Aberdeen Royal Infirmary, and the Data Monitoring and Safety Committee group (see bmj.com).

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community survey of older people in the same region of Scotland.¹⁰

Our participants were similar in age and place of residence to those studied in a previous, disputed trial that reported beneficial effects from supplementation.^{3 5 6} Participants in that trial had levels of nutrient deficiencies (assessed by blood sampling) similar to people designated by our questionnaire as being at high risk of nutrient deficiency. Unlike our trial, the supplement used in the previous trial had four times the levels of vitamin E and vitamin B₁₂ and also contained selenium, magnesium, calcium, and β carotene.³

Other randomised controlled trials have not found beneficial effects of multivitamin and multimineral supplements on risk of infection in community dwelling older people.¹⁴⁻¹⁶

Supplementation, especially of trace elements, has been shown to reduce infections in older people in nursing care with higher levels of nutritional deficiency.¹⁷ The effects of supplementation with vitamin E also seem to differ between community and nursing populations. In one study, vitamin E seemed to worsen the severity of infections in people living in the community,¹⁵ whereas it reduced the number of respiratory tract infections in a trial of nursing home residents.¹⁸

We cannot exclude the possibility that the intakes provided in the supplement were inadequate to affect the immune system. Our trial was pragmatic, which examined participants' self reported infections and use of health services rather than confirming infection by rigorous criteria seldom used in practice.

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