Efficacy of vitamin and antioxidant supplements in prevention of cardiovascular disease: systematic review and meta-analysis of randomised controlled trials

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- Research: Effects of B vitamins and omega 3 fatty acids on cardiovascular diseases (*BMJ* 2010;341:c6273)
- Research: Calcium supplements with or without vitamin D and risk of cardiovascular events (*BMJ* 2011;342:d2040)
- Research: Effects of vitamin E on stroke subtypes (*BMJ* 2010;341:c5702)

STUDY QUESTION Are vitamin and antioxidant supplements beneficial for the prevention of cardiovascular diseases?

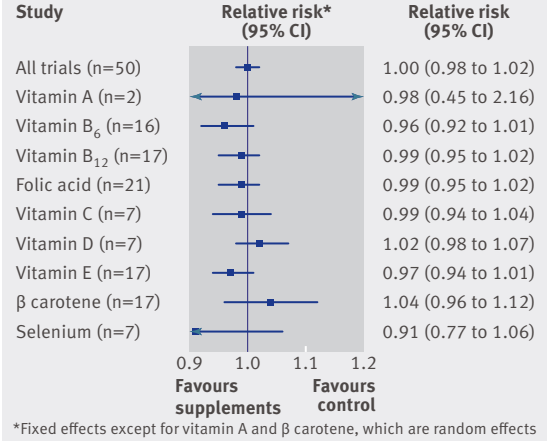
SUMMARY ANSWER Our meta-analysis of randomised controlled trials found no evidence to support the use of vitamin and antioxidant supplements in the prevention of cardiovascular diseases.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS
Previous randomised controlled trials have reported inconsistent findings regarding the efficacy of vitamin and antioxidant supplements in prevention of cardiovascular diseases, and there has been no published comprehensive meta-analysis. We found no evidence to support the use of vitamin or antioxidant supplements in the primary or secondary prevention of major cardiovascular events.

Selection criteria for studies
We searched PubMed, Embase, the Cochrane Library, Scopus, CINAHL, and ClinicalTrials.gov in June and November 2012. We included randomised controlled trials reporting the efficacy of vitamin or antioxidant supplements for the prevention of cardiovascular diseases.

Primary outcomes
Major cardiovascular events such as cardiovascular death, fatal or non-fatal myocardial infarction, angina, sudden cardiac death, fatal or non-fatal stroke, and transient ischaemic attack. Data were collected for subgroup analyses by type of prevention (primary *v* secondary), type of vitamins and antioxidants, dose of supplement, type of cardiovascular outcomes, study design, methodological quality (high *v* low), duration of treatment (<5 years *v* ≥5 years), funding source (independent organisation *v* pharmaceutical industry), provider of supplements (pharmaceutical industry *v* not pharmaceutical industry), type of control (placebo *v* no placebo), number of participants in each trial (<10 000 *v* ≥10 000), and supplements given singly or in combination with other vitamin or antioxidant supplements.

Overall efficacy of vitamin and antioxidant supplements on risk of cardiovascular diseases



*Fixed effects except for vitamin A and β carotene, which are random effects

Main results and role of chance
Out of 2240 articles retrieved from databases and relevant bibliographies, we included 50 randomised controlled trials with 294 478 participants (156 663 in intervention groups and 137 815 in control groups) in the final analyses. In a fixed effects meta-analysis of 50 randomised controlled trials, supplementation with vitamins and antioxidants was not associated with a reduced risk of major cardiovascular events (relative risk 1.00, 95% confidence interval 0.98 to 1.02; I^2=42). Overall, there was no beneficial effect of these supplements in the subgroup meta-analyses by type of prevention, type of vitamins and antioxidants, type of cardiovascular outcomes, study design, methodological quality, duration of treatment, funding source, provider of supplements, type of control, number of participants in each trial, and supplements given singly or in combination with other supplements. Among the subgroup meta-analyses by type of cardiovascular outcomes, vitamin and antioxidant supplementation was associated with a marginally increased risk of angina pectoris, while low dose vitamin B_6 supplementation was associated with a slightly decreased risk of major cardiovascular events. Those beneficial or harmful effects disappeared in subgroup meta-analysis of high quality randomised controlled trials within each category. Also, even though supplementation with vitamin B_6 was associated with a decreased risk of cardiovascular death in high quality trials, and vitamin E supplementation with a decreased risk of myocardial infarction, those beneficial effects were seen only in randomised controlled trials in which the supplements were supplied by the pharmaceutical industry.

Bias, confounding, and other reasons for caution
Our findings could not be directly applied to fruit and vegetables rich in natural vitamins or antioxidants or natural vitamins derived or extracted from plants because we investigated only synthetic vitamin and antioxidant supplements. We were also unable to evaluate whether vitamin and antioxidant supplementation would be beneficial against cardiovascular diseases for populations who are deficient in vitamins or antioxidants at baseline.

Study funding/potential competing interests
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Benefits of β blockers in patients with heart failure and reduced ejection fraction: network meta-analysis

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bmj.com
- Research: Effect of β blockers in treatment of chronic obstructive pulmonary disease (*BMJ* 2011;342:d2549)
- Clinical review: β blockers in hypertension and cardiovascular disease (*BMJ* 2007;334:946)

STUDY QUESTION

Is the effect of β blockers in patients with heart failure with reduced ejection fraction a class effect?

SUMMARY ANSWER

The benefits of β blockers in patients with heart failure with reduced ejection fraction seem to be mainly due to a class effect.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

The efficacy of β blockers in heart failure is well known. No statistical evidence from current trials data supports the superiority of any single agent over the others.

Selection criteria for studies

We included randomized trials that compared β blockers with other β blockers or other treatments in patients with heart failure with reduced ejection fraction and that reported mortality. We excluded studies if they were non-randomized, had less than 100 patients, or had a follow-up of less than three months.

Primary outcome(s)

The primary endpoint was death from any cause at the longest available follow-up assessed with odds ratios and Bayesian random effect 95% credible intervals, with independent extraction by observers.

Main results and role of chance

As expected, in the overall analysis, β blockers provided credible mortality benefits in comparison with placebo or standard treatment after a median of 12 months (odds ratio 0.69, 95% credible interval 0.56 to 0.80). However, we found no credible differences when comparing the different β blockers head to head for the risk of death, sudden cardiac death, death due to pump failure, or drug discontinuation. Accordingly, improvements in left ventricular ejection fraction were also similar irrespective of the individual study drug.

Bias, confounding, and other reasons for caution

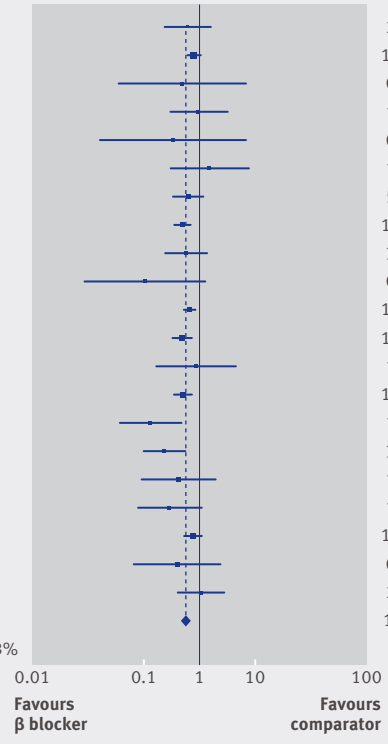
Paucity of data for some β blockers and inherent weaknesses of the constituent trials may limit the generalizability of our findings.

Study funding/potential competing interests

None.

Standard pair-wise meta-analysis of β blockers and effect on mortality in chronic heart failure

Study or subgroup	Events/total: β blocker	Events/total: Comparator	Odds ratio (Mantel–Haenszel, random) (95% CI)	Weight (%)	Odds ratio (Mantel–Haenszel, random) (95% CI)
ANZ 1997	20/207	26/208		2.8	0.75 (0.40 to 1.39)
BEST 2001	411/1354	449/1354		14.0	0.88 (0.75 to 1.03)
Bristow 1994	4/105	2/34		0.4	0.63 (0.11 to 3.62)
CARMEN 2004	14/191	14/190		1.9	0.99 (0.46 to 2.15)
Carvedilol Efficacy/Cohn	2/70	3/35		0.3	0.49 (0.07 to 3.60)
CHRISTMAS 2003	8/193/	6/194		1.0	1.35 (0.46 to 3.98)
CIBIS 1994	53/320	67/321		5.5	0.75 (0.50 to 1.12)
CIBIS II 1999	156/1327	228/1320		11.2	0.64 (0.51 to 0.79)
CIBIS III 2005	23/505	32/505		3.4	0.71 (0.41 to 1.22)
Colucci 1996	2/232	5/134		0.4	0.22 (0.04 to 1.17)
COMET 2003	512/1511	600/1518		14.7	0.78 (0.68 to 0.91)
COPERNICUS 2001	130/1156	190/1133		10.3	0.63 (0.49 to 0.80)
ENECA 2005	7/134	7/126		1.0	0.94 (0.32 to 2.75)
MERIT HF 2000/2002	145/1990	217/2001		11.2	0.65 (0.52 to 0.81)
MOCHA/Bristow 1996	12/261	13/84		1.6	0.26 (0.12 to 0.60)
Packer 1996	22/696	31/398		3.3	0.39 (0.22 to 0.68)
PRECISE 1996	6/133	11/145		1.1	0.58 (0.21 to 1.60)
RESOLVD 2000	8/214	17/212		1.5	0.45 (0.19 to 1.06)
SENIORS 2005	169/1067	1921061		10.9	0.85 (0.68 to 1.07)
Sturm et al 2000	5/51	8/49		0.8	0.56 (0.17 to 1.84)
Waagstein-MDC 1993	23/194	21/189		2.7	1.08 (0.57 to 2.20)
Total (95% CI)	1732/11 911	2138/11 211		100	0.71 (0.64 to 0.80)
Test for heterogeneity: τ^2=0.02, χ^2=29.84, df=20, P=0.07, I^2=33%					
Test for overall effect: z=5.96, P<0.001					
With prediction interval (0.58 to 0.84)					



Effectiveness of PhysioDirect telephone assessment and advice services for patients with musculoskeletal problems: pragmatic randomised controlled trial

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STUDY QUESTION Are PhysioDirect services, based on initial telephone assessment and advice from a physiotherapist, as effective as usual care involving patients waiting for a face-to-face appointment?

SUMMARY ANSWER Patients allocated to PhysioDirect received treatment more quickly than those allocated to usual care, and had equivalent clinical outcomes.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS PhysioDirect services have been introduced to improve access to physiotherapy, but it is unknown whether they are clinically effective. In this study, clinical outcomes from PhysioDirect were equivalent to those from usual care; although patients received PhysioDirect treatment more quickly, the service was not associated with increased patient satisfaction.

Design
We conducted a pragmatic randomised controlled trial to assess equivalence in clinical effectiveness between PhysioDirect and usual care. Patients allocated to PhysioDirect were invited to telephone a physiotherapist for initial assessment and advice, followed by face-to-face physiotherapy if necessary. Patients allocated to usual care joined a waiting list for face-to-face treatment. Patients were individually randomised 2:1 to PhysioDirect or usual care using an automated remote system. Outcomes were collected blind to group allocation.

Participants and setting
Adults referred by general practitioners or self referred for musculoskeletal physiotherapy to one of four physiotherapy services in England.

Primary outcome(s)
Primary outcome was the SF-36v2 physical component score (PCS) at six month follow-up (equivalence was prespecified as a between group difference of ≤2 in PCS). Secondary outcomes included four other measures of health outcome, number of appointments, waiting time for treatment, rates of non-attended appointments, time lost from work, and patient satisfaction and preference.

Main results and the role of chance
Of 1506 patients allocated to PhysioDirect and 743 to usual care, 85% provided primary outcome data at six months (1283 and 629 patients, respectively). PhysioDirect patients had fewer face-to-face appointments than usual care patients (mean 1.91 *v* 3.11; incidence rate ratio 0.59 (95% confidence interval 0.53 to 0.65)), a shorter waiting time (median 7 days *v* 34 days; arm time ratio 0.32 (0.29 to 0.35)), and lower rates of non-attendance (incidence rate ratio 0.55 (0.41 to 0.73)). At six months' follow-up, the SF-36v2 PCS was equivalent between groups (adjusted difference in means −0.01 (−0.80 to 0.79)). All measures of health outcome suggested a trend towards slightly greater improvement in the PhysioDirect arm at six weeks' follow-up and no difference at six months. There was no difference in time lost from work. Patients offered PhysioDirect were no more satisfied with access to physiotherapy than those offered usual care, but were slightly less satisfied with the service overall at six months (difference in satisfaction −3.8% (−7.3% to −0.3%; P=0.031). PhysioDirect patients were more likely than usual care patients to prefer PhysioDirect in future. We did not detect any adverse events or other harms.

Bias, confounding, and other reasons for caution
The few differences observed between groups were small and might not be clinically meaningful. Only 50% of eligible patients chose to take part in the study. Questions about satisfaction were only completed by patients who had contacted a physiotherapist.

Generalisability to other populations
Broad eligibility criteria meant that the results were generalisable to the types of patients likely to be offered PhysioDirect. Some people could have declined participation in the trial because they did not think PhysioDirect was suitable, so the findings might only be generalisable if PhysioDirect is offered to patients as a choice.

Study funding/potential competing interests
The study was funded by the Medical Research Council (MRC) and managed by the National Institute for Health Research (NIHR) on behalf of the MRC-NIHR partnership. The authors have no competing interests.

Trial registration number
Current Controlled Trials ISRCTN55666618.

Between group differences in SF-36v2 PCS

Time after randomisation	Mean score (standard deviation), sample size		Difference (95% CI)*	P
	Usual care	PhysioDirect		
6 weeks	41.81 (10.30), 653	41.57 (10.26), 1332	0.42 (−0.28 to 1.12)	0.24
6 months	44.18 (10.84), 629	43.50 (10.94), 1283	−0.01 (−0.80 to 0.79)	0.99

*Adjusted for outcome at baseline, sex, age, referral problem, and primary care trust.

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- Research: Effect of offering different levels of support and free nicotine replacement therapy via an English national telephone quitline (*BMJ* 2012;344:e1696)
- Research: Telemonitoring or structured telephone support programmes for patients with chronic heart failure (*BMJ* 2007;334:942)
- Research: Effect of telephone contact on further suicide attempts in patients discharged from an emergency department (*BMJ* 2006;332:1241)

Maternal and fetal risk factors for stillbirth: population based study

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Research: Association between maternal sleep practices and risk of late stillbirth (*BMJ* 2011;342:d3403)
Research: Contribution of smoking during pregnancy to inequalities in stillbirth and infant death in Scotland 1994-2003 (*BMJ* 2009;339:b3754)

STUDY QUESTION

What are the main risk factors for stillbirth in early and late pregnancy and what proportion of deaths are preventable?

SUMMARY ANSWER

Maternal obesity, maternal smoking, and fetal growth restriction are potentially modifiable risk factors that together accounted for 56% of stillbirths in our cohort, with fetal growth restriction the largest risk factor.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Stillbirth rates have shown little if any improvement since the early 1990s, and most have conventionally been considered unexplained and unavoidable, with only relatively weak risk factors known at the beginning of pregnancy. We found that growth restriction represents a strong risk factor, which is potentially avoidable through improved antenatal recognition and timely delivery. Extrapolated to the whole UK population, the effect of improved detection would result in 600 fewer stillbirths each year.

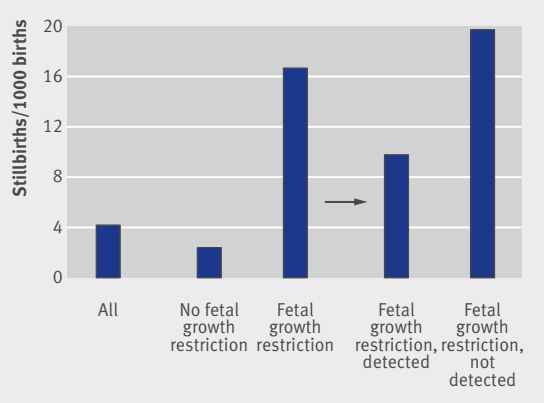
Participants and setting

Singleton and normally formed (excluding congenital anomalies) but otherwise unselected pregnancies in the West Midlands National Health Service region, England.

Design, size, and duration

Cohort study of 92 218 births including 389 stillbirths over a two year period (June 2009 to May 2011).

Stillbirth rate in relation to fetal growth restriction and whether or not it was detected antenatally



Main results and the role of chance

Multivariable analysis identified a risk of stillbirth for parity (para 0 and ≥3), ethnicity (African, African-Caribbean, Indian, and Pakistani), maternal obesity (body mass index ≥30), smoking, pre-existing diabetes, history of mental health problems, and complications during pregnancy including antepartum haemorrhage and fetal growth restriction. The presence of fetal growth restriction constituted the highest adjusted relative risk, and this applied to pregnancies where mothers did not smoke (7.8, 95% confidence interval 6.6 to 10.9), smoked (5.7, 3.6 to 10.9), and were exposed to passive smoke only (10.0, 6.6 to 15.8). Fetal growth restriction also had the largest population attributable risk for stillbirth and was fivefold greater when it was not detected antenatally than when it was (32.0 *v* 6.2%). In total, 195 of the 389 stillbirths in this cohort had fetal growth restriction, but in 160 of these cases (82%) fetal growth restriction had not been detected antenatally. When fetal growth restriction was detected antenatally delivery was 10 days earlier than when it was not detected: median 270 (interquartile range 261-279) days *v* 280 (273-287) days. The stillbirth rate (per 1000 births) was 4.2 overall, 2.4 in pregnancies without fetal growth restriction, 9.7 when fetal growth restriction was detected antenatally, and 19.8 when fetal growth restriction was not detected.

Bias, confounding, and other reasons for caution

The database used was comprehensive and allowed adjustment for the known factors associated with stillbirth. The majority of the growth restricted stillbirths do not have a postmortem examination, nor a diagnosis based on antenatal investigation, because fetal growth restriction was not suspected antenatally. We estimated the time of death as on average two days before delivery, and identified fetal growth restriction as being below the 10th gestation related optimal weight centile, which identifies pathological smallness by adjusting for maternal characteristics and calculating the fetal growth potential for each pregnancy.

Generalisability to other populations

The findings are based on a heterogeneous, unselected cohort and are therefore generalisable to other maternity populations within similar healthcare systems.

Study funding/potential competing interests

No external funding was received. We have no competing interests.