Primary prevention of cardiovascular disease: an umbrella review of non-pharmacological interventions

Prevención primaria de enfermedades cardiovasculares: una revisión de revisiones de intervenciones no farmacológicas

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ABSTRACT

Background. The aim of this study is to determine the effectiveness of non-pharmacological interventions for prevention of cardiovascular disease (CVD) events and mortality in healthy adults or those at high risk of CVD.

Methods. An umbrella review about primary prevention of non-pharmacological interventions was undertaken in key databases as PubMed Health, Effective Health Care Program AHRQ, McMaster University and the Cochrane Plus until July 2017. The primary outcomes were the relative risk of fatal and non-fatal CVD events, and mortality. Secondary outcomes were adverse events.

Results. Twenty-four reviews were included of which thirteen reported outcomes of interest. Four of these found a pooled statistically significant risk reduction: dietary supplements of vitamin D, increased consumption of omega 3 fatty acids, Qigong, and counselling or education to modify more than one cardiovascular risk factor. Seven studies reported adverse events but minor or insignificant with respect to the control group.

Conclusions. Four non-pharmacological interventions have been shown to provide a statistically significant reduction in risk of CVD events or overall mortality, with minor adverse events if any. Further research should aim for higher methodological quality and longer follow-up of interventions to establish if these interventions, alone or in combination, translate into definite long-term health benefits.

Keywords. Cardiovascular. Non-prescription intervention. Umbrella review. Systematic reviews and meta-analyses.

RESUMEN

Fundamento. El objetivo de este estudio es determinar la efectividad de intervenciones no farmacológicas para la prevención de eventos relacionados con enfermedad cardiovascular (CVD), y mortalidad en adultos sanos o con alto riesgo de CVD.

Método. Revisión de revisiones sobre prevención primaria de intervenciones no farmacológicas en las bases de datos de PubMed Health, Effective Health Care Program AHRQ, McMaster University y la Cochrane Plus hasta Julio de 2017. Los resultados primarios fueron el riesgo relativo de eventos CVD, fatales y no fatales, y de mortalidad; los efectos adversos fueron los eventos secundarios.

Resultados. Se incluyeron veinticuatro revisiones, de las cuales trece informan resultados de interés. Cuatro observaron una reducción significativa del riesgo: suplementación de vitamina D, incremento del consumo de ácidos grasos omega 3, Qigong, y educación para la modificación de factores de riesgo cardiovascular. Siete revisiones informaron sobre eventos adversos menores y/o no significativos respecto del grupo control.

Conclusiones. Cuatro intervenciones no farmacológicas son las que muestran una reducción estadísticamente significativa en eventos CVD o mortalidad total, con escasos o nulos efectos adversos. Se requiere de una investigación de mayor calidad metodológica y de mayor seguimiento de las intervenciones para establecer si estas, combinadas o por separado, conducen a claros beneficios en salud a largo plazo.

Palabras clave. Cardiovascular. Intervención no-prescrita. Revisión de revisiones. Revisiones sistemáticas y meta-análisis.

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INTRODUCTION

Statins and other pharmacological interventions are now widely recommended as primary prevention against cardiovascular disease (CVD)[1]. Yet while statins were initially recommended for high-risk individuals, this threshold has steadily been reduced. For example, guidelines from the National Institute for Care Excellence imply that ten million healthy individuals in the UK, with no previous history of CV events, are now candidates for taking statins for primary prevention[2]. This has led to concerns about potential long term risks and over-medicalization[3].

Consequently, attention is shifting to non-pharmacological interventions for primary prevention, which many perceive as more appropriate for healthy individuals, with less risk of harm, and possibly with lower overall cost than statins to the public health system. Undoubtedly, tobacco cessation, reducing dietary fats and increasing physical activities have played a part in reducing rates of CVD[4-5]. According to the WHO, appropriate policy and environmental changes could bring about further major reductions. Nevertheless, there is less evidence about which non-pharmacological interventions led by primary care professionals have been shown effective for CVD risk reduction in the general population as an alternative (or complement) to widespread use of statins.

Many candidate non-pharmacological interventions have been studied, including dietary advice, food supplements with vitamins or minerals, physical exercise, mental exercises and general health checks. The objective of this study is to determine the effectiveness of non-pharmacological interventions for prevention of cardiovascular disease and mortality in people with no history of CVD events. We apply an umbrella review methodology. This is a "review-of-reviews", providing a balanced summary of evidence from several systematic reviews of randomised controlled trials. This enables us to take a broad view of the state of the evidence at a given point in time across a wide range of different treatments. The study is carried out according to methodological recommendations from the Joanna Briggs Institute[6] and Smith et al[7].

MATERIALS AND METHODS

The research question was to determine the relative effectiveness of non-pharmacological interventions to prevent major CVD events and mortality in adult classified as having no previous history of CVD events or at risk of developing CVD, compared to placebo or no intervention.

The design of the study, an umbrella review of the literature, was carried out. The protocol was registered in PROSPERO (CRD 42015016447 http://www.crd.york.ac.uk).

The search was conducted using PubMed Health, Effective Health Care Program Agency for Healthcare Research and Quality (AHRQ), Health Evidence and the Cochrane Plus databases; and using as free terms: *"primary prevention", "cardiovascular disease", "review"*. In addition, the reference lists of the included articles were examined. Only papers in English or Spanish and published by 30th July 2017 were included.

Inclusion criteria:
– systematic reviews of randomized clinical trials (with or without meta-analysis)
– adult classified as having no history of CVD events, or at risk of developing CVD events or those of general population
– intervention: Non-pharmacological for targeted interventions to improve cardiovascular health in primary prevention. Any duration or time of follow- up periods were considered
– comparing group: placebo or no intervention
– outcomes intended to be measured: overall mortality, cardiovascular mortality, cardiovascular events, and adverse events related with the interventions

Exclusion criteria:
– systematic reviews conducted only in populations with specific conditions (only smokers, only obese people)
– reviews which mix primary and secondary prevention populations together

– review which mix results of clinical trials with other designs
– systematic reviews of quasi-experimental designs

Identification of the reviews was carried out by two reviewers (EMR and AOL) who selected independently all the works and checked both title and abstract against the inclusion and exclusion criteria. Any discrepancies were agreed by consensus or third researcher (DE). Any duplicate articles were subsequently excluded. Articles were managed using Reference Manager Software.

Following the definitive selection of the articles of interest, two researchers carried out an independent evaluation of the methodological quality of each review (EM and AOL). To achieve this, the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) checklist with eleven items was used[8]. Any discrepancies were discussed and agreed by consensus.

A data extraction form was developed to record bibliographic information. The general characteristics of the study (participants included, description of intervention) and outcome data (including details of outcome assessment and adverse effects) were extracted from each included study. In those articles that reported data for both primary and secondary prevention,

we extracted only the primary prevention results.

The authors carried out a qualitative synthesis of results from included reviews, the interventions were classified according to focus of intervention (proposed by the authors), and type of outcomes (all-cause mortality, cardiovascular mortality, both fatal or non-fatal CVD events and adverse events). Heterogeneity between studies was evaluated using Higgin's I^2, where $I^2 >50\%$ imply a substantial level of heterogeneity[9]. A random-effects model was used to combine study-specific relative risk (RR) and calculate a 95% confidence interval (CI). The analyses were performed with Stata software version 11.

RESULTS

The initial search yielded a total of 643 publications. After excluding by title and/or abstract, a total of 127 full-text works were assessed for eligibility (see Figure 1). One review[10] was excluded in order to avoid duplicity, as it had the same aim and higher risk of bias than another included review[11]. Finally, twenty-four reviews were included in the final synthesis (Fig. 1), of which thirteen reported CVD events and/or overall mortality as primary outcome.
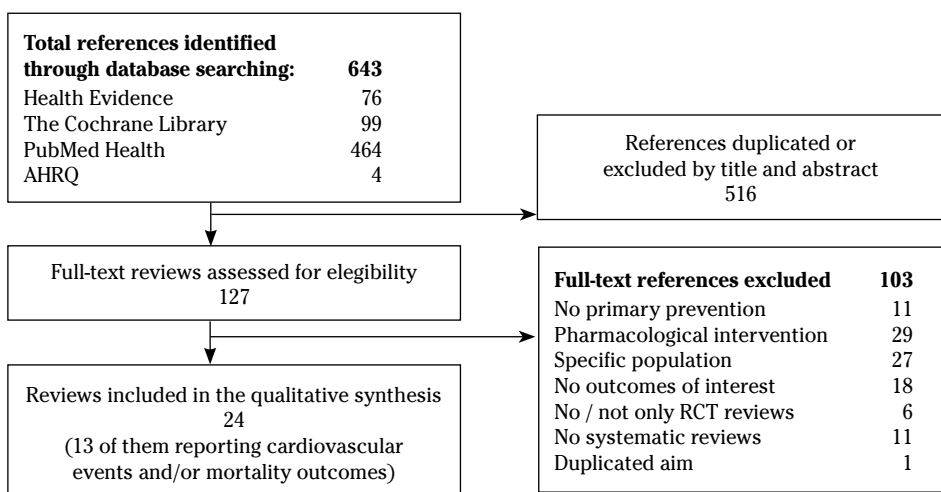

Figure 1. Flow diagram for review.

Primary prevention

Eight types of non-pharmacological interventions for primary prevention of CVD were reviewed (Table 1):

– supplements: vitamin C[12], antioxidant[13], vitamin D[14], selenium[15], vitamin Co-enzyme Q10[16], vitamin K[17], and vitamin, mineral and multivitamin supplements[18]. Fortmann's review[22] included different interventions based on single and paired combination of supplementation with vitamins and minerals supplementation, including vitamin C and selenium. The two reviews on vitamin C[12,18] shared elements such as type of population included and intervention, but they differed in both the outcome measures included and some inclusion criteria (minimum follow-up time for required randomized controlled trials (RCT) (three months)[12], trials with *good* or *fair* quality, studies carried out in countries whose Human Development Index was considered *very high*[18])

– dietary interventions: advice to reduce dietary salt[19], advice to increased consumption of fruit and vegetables[20] and *Mediterranean* dietary pattern[21]

– diet supplementation: nuts, green and black tea[23], dietary fibre[24], Omega 3[25] and Omega 6[26] fatty acids

– multiple risk factor interventions: counseling or education to modify more than one cardiovascular risk factor[11,27], the last of them in low income countries

– physical exercise: exercise training[28], Qigong[29], Tai chi[30], Yoga[31]

– mental exercise: transcendental meditation[32]

– digital health intervention[33]

– general health checks[34]

Twenty-two reviews were published by the Cochrane collaboration and two by other groups[18,33], all during the last five years, except two reviews from 2004[20,25] were not published in the last five years (Table 1). The overall number of participants included in these systematic reviews ranged between 60 participants

Table 1. Characteristics of the reviews included and adverse events

Author Year	Intervention Comparison	Population	Outcomes	Studies Participants	Follow-up Range	Characteristics of Participants	AE
Al-Khudairy 2017[12]	supplements of vit.C alone, at any dose or frequency *vs.* placebo / no intervention	-healthy adults from GP -adults at moderate / high risk of CVD	-all-cause mortality -CVD mortality -non-fatal end points[a]	8 15,445	≥3 months 3m-8y	14,641 male physicians aged ≥50 with CVD risk factors (n=1), men and women (n=6), no specified gender (n=1)	reported but no specified (n=2)
Bjelakovic 2012[13]	antioxidant supplements (carotene, vit.A, vit.C, vit.E, and selenium)[b] at any dose, duration and route of administration *vs.* placebo / no intervention	-healthy adults -adults from GP	-all-cause mortality	26 215,900	NA	NA	NS
Bjelakovic 2014[14]	supplements of vit.D, alone or combined with calcium, at any dose or duration[b] *vs.* placebo / no intervention[c]	-healthy adults from GP irrespective of serum vit.D	-all-cause mortality -CVD mortality -AE	48 94,491	NA	healthy volunteers (n=4), postmenopausal women (n=9), older people (n=35)	NA

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Author Year	Intervention Comparison	Population	Outcomes	Studies Participants	Follow-up Range	Characteristics of Participants	AE
Rees 2013[15]	supplements of selenium alone *vs.* placebo / no intervention	-adults from GP -adults at high risk of CVD	-all-cause mortality -major CVD events (CVD, MI, non-fatal stroke, revascularisation procedures as CABG or PTCA) -CHD events (fatal CHD, non-fatal MI) -stroke events (fatal and non-fatal stroke, PAD)	12 19,715	≥3 months 1-2w-12y	17,843 men (n=6), healthy population (n=3), prostate cancer (n=1), at high risk of cancer (n=2)	increased risk [d] of DM2 (1.06, 0.97-1.15; n=3) or alopecia (1.28, 1.01-.62) and 1-2 grade dermatitis (1.17, 1.0-1.35; n=1)
Flowers 2014[16]	supplements of co-enzyme Q10 alone *vs.* placebo / no intervention	-adults aged ≥18 from GP -adults at high risk of CVD	-all-cause mortality -CVD mortality -non-fatal endpoints** -AE	6 218	≥12 weeks 12-16w	men and women (n=5), no specified gender (n=1), at high risk of CVD (n=6; obese n=1, hypercholesterolemic n=4, hypertensive n=1)	NR
Hartley 2015[17]	supplements of vit.K alone *vs.* placebo / no intervention	-healthy adults aged ≥18 from GP -adults at moderate / high risk of CVD	-all-cause mortality -CVD mortality -non-fatal endpoints[a] -AE	1 60	≥3 months	healthy men and women aged 40-6 with BMI=18.5-30	NR
Fortmann 2013[18]	supplements of vitamins (A, C, D, E) and minerals (calcium, folic acid, carotene, selenium)[b,e] alone or combined *vs.* placebo / no multivitamin	-adults from GP with no history of CVD	-all-cause mortality -CVD events	24 NS	≥6 months 6m-16y (most studies ≥ 10y)	NA	trivial AE related to vit. A (n=1)
Hooper 2004[19]	advice to reduce sodium intake *vs.* placebo / no intervention	-healthy adults aged ≥16 with normal / raised blood pressure	-total mortality -combined CVD events (fatal and non-fatal MI, stroke, angina, heart failure, peripheral vascular events, sudden death, non-scheduled CVD interventions as CABG, PTCA)	11 3,514	≥26 months 6m-7y	2,326 healthy normotensive adults mostly white, male, mean age 40 (n=3), 387 untreated hypertensive adults aged 16-64 (n=5), 801 treated hypertensive aged 55-67 (n=3)	NS
Hartley 2013[20]	advice to increase consumption of fruit and vegetables (or provision of them) *vs.* no /minimal intervention[a]	-healthy adults aged ≥18 -adults at high risk of CVD[f]	-all-cause mortality -CVD mortality -non-fatal endpoints[a] -AE	10 1,730	≥3 months 3-12m	only women (n=1), healthy post-menopausal women with family breast cancer history (n=1), women with metabolic syndrome (n=2), healthy adults (n=3), adults with LDL=130- 190 mg/dL and triglyceride ≤250 mg/ dL (n=1), obese (n=1), with colorectal adenomatous polyps in the last 5y (n=1), pre-metabolic or healthy (n=1)	increased bowel movements, bad breath and body odor (n=3)
Rees (2013)[21]	Mediterranean dietary pattern[g] *vs.* no / minimal intervention[h]	-adults from GP -adults at high risk of CVD[f]	-all-cause mortality -CVD mortality -non-fatal endpoints[a] -AE	11 52,044	≥3 months 3-8y	48,835 women (n=1), 49,185 healthy adults (n=5)	NR

Author Year	Intervention Comparison	Population	Outcomes	Studies Participants	Follow-up Range	Characteristics of Participants	AE
Martin (2015)[22]	advice to increase consumption of nuts (or provision of them) vs. no / minimal intervention	-adults from GP with no history of CVD[e]	-all-cause mortality -CVD mortality -non-fatal endpoints[a] -AE	5 435	≥3 months 3-6m	women, mean age=37.4-54.3 (n=1)	allergic reaction to nuts (n=1), insignificant weight gain (n=1)
Hartley (2013)[23]	intake of green / black tea extracts or as a beverage vs. no / minimal intervention[h] / placebo	-healthy adults -adults at high risk of CVD[f]	-all-cause mortality -CVD mortality -non-fatal endpoints[a] -AE	11 821	≥6 months 3m-2y	women (n=4), postmenopausal women with osteopenia (n=1), breast cancer survivors (n=1); either DM or two other CVD risk factors (n=1), up to moderate hypercholesterolemia (n=2), healthy participants (n=6)	prostate cancer, appendicitis, hospitalization for influenza, and retinal detachment (n=5, unlikely attributable to intervention)
Hartley (2016)[24]	advice to increase dietary fibre consumption (or provision of fibre supplements / high-fibre foods) vs. no/minimal intervention	-adults from GP -adults at high risk of CVD	-all-cause mortality -CVD mortality -non-fatal endpoints[a] -AE	23 1,513	≥3 months NS	healthy participants (n=4), over weighted or obese (n=6), with clear signs of metabolic syndrome (n=3), hypertensive (n=3), women with climacteric symptoms (n=1)	n=14; gastrointestinal events (flatulence and diarrhoea, n=1; flatulence but also constipation, nausea, bloating and diarrhoea, n=7; decrease of antihypertensive medication side-effects scores from baseline observed only in the intervention group (n=1)
Hooper (2004)[25]	advice on diet or provide a diet to increase 3FA by foodstuffs or supplements (oil / capsule)[e] vs. placebo / no advice / no supplementation / usual diet	-adults at any risk of CVD	-all-cause mortality -fatal and non-fatal CVD events (MI, angina, stroke, heart failure, peripheral vascular disease, sudden death, CABG, PTCA) -cancer -AE	48 35,140	≥6 months 11-48 m	at high (n=21), moderate (n=10) or low risk (n=17) of CVD; male proportion ≥70% (n=24), 31-69% (n=17), 0-30% (n=5), not stated (n=2); mean ages in the 30s (n=6), 40s (n=7), 50s (n=27), 60s (n=4), 80s (n=3), unclear (n=1)	not significant thrombophlebitis (1.59, 0.72-3.51, n=1), urolithiasis (0.80, 0.47-1.36, n=1) and DM (0.87, 0.15- 5.08, n=2)[d]
Al-Khudairy (2015)[26]	advice on diet, supplementation or provide a diet to increase / decrease 6FA vs. placebo / no advice / no supplementation / usual diet	-healthy adults from GP -adults at moderate / high risk of CVD	-all-cause mortality -CVD mortality -non-fatal endpoints[a] -AE	4 664	≥6 months	over weighted or obese healthy participants aged 35-65 (n=1) and 40-70 (n=1), older men and post-menopausal women aged 45-70 (n=1), adults aged 23-58 with hypercholesterolemia (n=1)	NR
Ebrahim (2011)[11]	health promotion activity (counseling or educational intervention, individually or by group, with or without pharmacological treatment) to achieve a behavioral change altering ≥1 CVD risk factor Parallel-group design	-adults (aged ≥35) from GP -adults from occupational groups -adults with specific risk factors[i]	-all-cause mortality -fatal CHD and stroke events -non-fatal CHD (MI, unstable angina, CABG, PTCA, stroke events)	55 139,256	≥6 months. 6m-12y (median=1 y)	mean age=50y; adults ≥60 (n=2), ≥75 (n=53); patients with DM (n=5) and with hypertension (n=16)	NS

Author Year	Intervention Comparison	Population	Outcomes	Studies Participants	Follow-up Range	Characteristics of Participants	AE
Uthman (2015)[27]	health promotion intervention (dietary advice, increasing activity, smoking cessation) with or without pharmacological treatment to achieve a behavioral change altering ≥1 CVD risk factor *vs.* no intervention	-adults from the workforce, including those at high-risk (or not) of CVD[f]	-CVD mortality -non-fatal endpoints[a] -AE	13 NS	≥6 months 6-30m (mean= 13.3m)	healthy or GP (n=2), high CVD risk groups (pre- and hypertensive, with metabolic syndrome, obese, with impaired glucose regulation) (n=11)	NR
Seron (2014)[28]	aerobic / resistance exercise training *vs.* no exercise	-people at high CVD risk with a Framingham risk score ≥10% over 10 y	-CVD mortality -all-cause mortality -MI -stroke	4 823	≥8 weeks 16w-6m	mean age=52.6y (n=4)	NR
Hartley (2015)[29]	any style of Qigong *vs.* no / minimal intervention (health or physical activity promotion without face-to-face interaction)	-healthy adults aged ≥18 years from GP -adults at high risk of CVD	-all-cause mortality -CVD mortality -non-fatal endpoints[a] -AE	11 1,369	≥3 months 3m-30y	men and women (n=5), men (n=4), not specified gender (n=2); healthy participants (n=2), elder with high blood lipids (n=1), hypertensive patients (n=8)	NR
Hartley (2014)[30]	any style of Tai chi *vs.* no / minimal intervention[h]	-healthy adults -adults at high risk of CVD	-all-cause mortality -CVD mortality -non-fatal endpoints[a] -AE	13 1,520	≥ 3 months 3-6m	men and women (n=9), only women (n=4); borderline (n=1) and essential (n=2) hypertensive, hypertensive with liver and kidney deficiency syndrome (n=1), hypertensive (n=1), older participants with high risk of falling (n=1), healthy people (903 participants, n=7)	NR
Hartley (2014)[31]	any type of yoga with postural exercises, breathing control and meditation *vs.* no / minimal intervention[a]	-healthy adults -adults at high risk of CVD	-all-cause mortality -CVD mortality -non-fatal endpoints[a] -AE	11 800	≥12 weeks 14w–8m	only man (n=1), only women (n=10), including healthy premenopausal (n=1), with metabolic syndrome (n=1), obese postmenopausal (n=1), with menstrual irregularities (n=1); essential hypertensive (n=1), males with high cholesterol and hypertension (n=1), HIV-infected participants (n=1), no yoga exercisers with family history of DM2 and at least one cardio-metabolic risk factor (n=1), healthy participants (n=3)	NR
Hartley (2014)[32]	transcendental meditation *vs.* no / minimal intervention[h]	-healthy adults -adults at high risk of CVD	-all-cause mortality -CVD mortality -non-fatal endpoints[a] -AE	4 430	≥3 months NS	men and women (**n**=3), only women (**n**=1); healthy participants (316 adults, **n**=1), essential hypertensive (**n**=1), older people (**n**=1)	NR

Author Year	Intervention Comparison	Population	Outcomes	Studies Participants	Follow-up Range	Characteristics of Participants	AE
Widmer (2015)[33]	digital health interventions [b,e] (telemedicine, web-based strategies, email, mobile phone, apps, text messaging, monitoring sensors) *vs.* no active intervention beyond usual care following standard guidelines	-adults at any risk of CVD	-CVD events -hospitalizations -all-cause mortality	2 1,055	≥1 month NS	hypertensive (n=1), over weighted adults (**n**=1)	NS
Krogsboll (2012)[34]	general health checks screening for ≥1 disease or risk factor and in more than one system by doctor, nurse or other health professional *vs.* control group	-GP or subgroups (employees from a company aged <65, or people with specific risk factors / diseases)	-all-cause mortality -disease-specific mortality -morbidity	14 182,880	4-22 y	no details of interest	NS

AE: adverse events; vit: vitamin; *GP: General Population; CVD: cardiovascular disease; m: months; y: years;* NA: not applicable as primary and secondary prevention data were mixed; NS: not studied; CHD: coronay heart disease; w: week; DM2: type 2 diabetes mellitus; NR: not reported; BMI: body mass index; ωFA: omega fatty acids.

[a]: *myocardial infarction (MI)*, *coronary artery bypass grafting* (CABG*), per cutaneous transluminal coronary angioplasty (PTCA),* angina, angiographically defined *coronary heart disease*, stroke, carotid endarterectomy, and *peripheral arterial disease (PAD);* [b]: *only primary prevention information/ results provided;* [c]: calcium in the control group was included if equally used in the vitamin D groups of the trial; [d]: relative risk and confidence interval at 5%; [e]: only information about random clinical trials; [f]: studies excluded if ≥25% participants had CVD; [g]: consumption of at least two of the following dietary factors: high monounsaturated/saturated fat ratio (use of olive oil as main cooking ingredient), low to moderate red wine consumption, high consumption of legumes, high consumption of grains and cereals, high consumption of fruits and vegetables, low consumption of meat and meat products and increased consumption of fish, moderate consumption of milk and dairy products; [h]: as leaflets with no person-to-person interaction or reinforcement; [i]: studies excluded if ≥25% participants had diagnosed CVD or DM2.

for vitamin K supplements[20] and 215,900 participants for antioxidant supplementation[13]. Only four reviews included less than 500 participants[16,17,22,32]. The number of trials per review ranged between one[17] and 55[19]. Most studies were carried out in developed countries, except one conducted in low- and middle-income countries[27]. Most reviews defined a minimum follow up time (between three and six months) for RCTs to be included; the maximum follow up time was up to 20-30 years[29].

Low risk of bias for nine of the eleven items included in the AMSTAR checklist (Appendix 1) was showed by all studies, exception made by five studies whose authors did not evaluate the risk of publication bias and/or report the results[18-20,22,28,34] (item 10). Eleven studies did not report outcomes of interest, preventing to combine results and, thus, scoring was not applicable.

Deaths from any cause

Several interventions showed some risk reduction in all-cause mortality[14,15,18,19,27,34,47]: reduce dietary salt[19], selenium supplementation[15,18], folic acid + vitamin D + calcium supplementation[18], general health checks[34], vitamin D supplementations[14] and practice of Qigong[29], but only the two last reached statistical significance (Table 2). The antioxidant supplements[13] showed a significant increase of 5% [95% CI 2-8%] for all-cause mortality risk.

Cardiovascular mortality

Both multiple risk factor interventions[11] and Qigong practice[29] showed pooled significant reductions in stroke mortality (risk reduction 25% [95% CI 5-40%] and 45% [95% CI 26-58%], respectively) (Table 3).

Table 2. Effect of the interventions on all-cause mortality

Intervention	Studies* N	Events N (%)	Effect RR (95%CI)	I² (%)
Antioxidant supplementation[13]	19	21,334 (12.0)	1.03 (0.97-1.08)[a, b]	43.0
	19	21,334 (12.0)	1.05 (1.02-1.08)[a, c]	46.9
	7	2,479 (6.6)	0.93 (0.84-1.03)[d,b]	0
Vitamin A supplementation[18]	1	115 (5.0)	1.15 (0.81-1.65)	NA
Vitamin C supplementation[12,18]	1	-	HR=1.07 (0.97-1.18)[e]	NA
	2	1,663 (11.2)	1.06 (0.97-1.16)	NI
Vitamin D supplementation[14]	48	11,955 (12.7)	**0.97 (0.9-0.99)[b]**	0
Vitamin D + Calcium supplementation[18]	1	1,551 (4.3)	0.92 (0.83-1.01)	NA
Calcium supplementation[18]	3	1,827 (23.8)	1.04 (0.96-1.12)	NI
Folic acid supplementation[18]	1	29 (2.8)	0.52 (0.24-1.10)	NA
Selenium supplementation[15,18]	2	1,336 (7.2)	0.97 (0.88-1.08)[c]	0
Omega 3 fatty acids[25]	44	1,995 (5.5)	0.87 (0.73-1.03)	0
Advice to reduce dietary salt[19]	4	17 (0.7)	0.90 (0.36-2.24)[a]	0
Qigong[29]	2	147 (28.8)	**0.54 (0.39-0.90)[a,f]**	0
General health checks[34]	9	11,940 (7.7)	0.99 (0.95-1.03)[c]	0
Multiple risk factor interventions[11]	14	2,511 (1.8)	OR=1.00 (0.96-1.05)[c]	62

*: number of included studies providing information of interest; RR: relative risk; I² : Higgins' heterogeneity; [a]: primary prevention trials with low risk of bias; [b]: random effects model analysis; [c]: fixed-effect model analysis; [d]: primary prevention trials with a high risk of bias; [e]: data from the clinical trial Physicians Health Study II (men aged ≥50); NA: not applicable; HR: hazard ratio; NI: No information; [f]: this data was calculated by the authors of the present review as it was not provided in the original review; OR: odds ratio. Effects in bold are statistically significant.

Table 3. Effect of the interventions on cardiovascular mortality

Intervention	Studies* N	Events N (%)	Effect RR (95%CI)	I² (%)
Vitamin C supplementation[12]	1	–	HR=1.02 (0.85-1.22)[a]	NA
Selenium supplementation[15]	2	342 (1.9)	0.97 (0.79-1.20)	44
Omega 3 fatty acids[25]	14	1,418 (4.3)	0.85 (0.68-1.06)	0
Advice to reduce dietary salt[19]	2	17 (2.3)	0.82 (0.56-1.21)[b]	0
Mediterranean dietary pattern[21]	1	–	HR=1.01 (0.81-1.27)[c,d]	NA
			HR=0.94 (0.65-1.35)[d,e]	NA
Qigong[29]	2	101 (19.8)	**0.55 (0.42-0.74)[b,e,f]**	1
General health checks[34]	8	4,567 (29.6)	1.03 (0.91-1.17)[g]	64
Multiple risk factor interventions[11]	11	901 (2.2)	OR=0.99 (0.92-1.07)[c,g]	32
	7	342 (0.6)	**OR=0.75 (0.60-0.95)[e,g]**	0

*: number of included studies providing information of interest; RR: relative risk; I² : Higgins' heterogeneity; HR: hazard ratio; [a]: data from the clinical trial Physicians Health Study II (men aged ≥50); NA: not applicable; [b]: random effects model analysis; [c]: coronary heart disease death; [d]: data from RCT WHI study (postmenopausal women); [e]: fatal stroke; [f]: this data was calculated by the authors of the present review as it was not provided in the original review; [g]: fixed-effect model analysis. Parameters in bold are statistically significant.

Cardiovascular events

The effect of interventions on CVD events, either a combined outcome of fatal and non-fatal events, or only non-fatal events are showed in table 4. A significant risk reduction of 16% [95% CI 2-23%] was found in multifactorial individual lifestyle interventions[11], despite substantial between-study heterogeneity. Subgroup analysis showed that the combined event relative risk was 0.71 (p<0.05) in patients with either hypertension or diabetes, while there was no significant effect on patients without co-morbidity.

Qigong[29] showed a significant reduction of stroke incidence (44% [95% CI 17-62%]).

Increased consumption (dietary or supplemental) of omega 3 fatty acids, showed a significant risk reduction of heart failure of 49% (95% CI 15-69%)[25].

Adverse events

Eight of the 24 included reviews reported adverse events related with the interventions: vitamin C[12], selenium[15] and mineral and multivitamin[18] supplements, increased consumption of fruits and vegetables[20], and also in nut[22], green and black tea[23] and dietary fibre[24] consumption (Table 1). Al-Khudairy et al[12] reported one RCT describing death, serious adverse events and adverse event without any further detail. In the other reviews, adverse events were a minor problem and/or the difference between the intervention and the control group was not statistically significant. In two reviews[18,21], the data regarding adverse events were aggregated, thus primary was indistinguishable from secondary prevention.

DISCUSSION

This umbrella review provides information about diverse interventions for the primary prevention of CVD events and mortality. Our work constitutes the first comprehensive and systematic summary of diverse non-pharmacological interven-

tions based on the umbrella review methodology. We included twenty-four reviews concerning non-pharmacological interventions; four of the thirteen reviews reporting CVD events or mortality found a significant reduction on them[11,14,25,29].

Ebrahim et al[11] found that individual lifestyle interventions significantly reduced stroke-related mortality and any CVD event (fatal and non-fatal). These interventions pursued a behavioural change in order to alter more than one cardiovascular risk factor (i.e. diet, reduce blood pressure, smoking, total blood cholesterol or increase physical activity) by means of counselling or educational interventions, with or without pharmacological treatments. They were commonly provided by a variety of health professionals (physicians, nurses, nutritionists, dieticians, personal trainers, cooks, psychotherapists and physiotherapists). Focusing multicomponent lifestyle interventions (dietary advice, smoking cessation, stress reduction, physical exercise, etc.) on individual risk factors -taking account of the characteristics of the patients and, furthermore, targeting at those most likely to benefit (for example, those with hypertension or diabetes)- is very important, as these interventions seem to not benefit patients without the risk factors[11].

Bjelakovic[14] found that vitamin D supplementation at any dose, for any duration, in monotherapy or in combination with calcium, administrated enteral or parenterally, significantly reduced all-cause mortality.

Hooper[26] found that omega-3 fatty acid intervention (dietary supplementation, a provided diet or advice on diet such that the product orally consumed as oil or capsule or as food stuffs had an omega 3 fat content of at least 10% of the total fat content) significantly reduced the risk of heart failure.

Finally, Hartley[29] found that Qigong significantly reduced stroke incidence, all-cause mortality and stroke-related mortality. Qigong is defined by the National Qigong Association[35] as *an ancient Chinese health care system that integrates physical postures, breathing techniques and focused intention*.

Systematic reviews included in this umbrella review were generally well conduct-

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Table 4. Effect of the interventions on all cardiovascular events (fatal and/or non-fatal)

Intervention	Studies[*] N	Events N (%)	Effect RR (95%CI)	I² (%)
Beta-Carotene supplementation[18]	2	2,157 (3.5)	1.01 (0.93-1.09)[a]	NI
Vitamin C supplementation[12,18]	1	–	HR=1.04 (0.87-1.24)[b,c]	NA
			HR=0.96 (0.86-1.07)[b,d]	NA
			HR=0.93 (0.84-1.03)[b,e]	NA
			HR=0.89 (0.74-1,07)[b,f]	NA
	1	1,245 (8.5)	0.99 (0.89-1.10)[a]	NA
Vitamin D supplementation[18]	2	1,682 (21.1)	0.94 (0.87-1.02)[a]	NI
Vitamin D + Calcium supplementation[18]	1	3,642 (10.1)	1.01 (0.95-1.07)[a]	NA
Calcium supplementation[18]	1	96 (10.3)	1.09 (0.75-1.60)[a]	NA
Vitamin E supplementation [18]	3	4,328 (6.0)	0.97 (0.92-1.03)[a]	NI
Selenium supplementation[15,18]	2	2,036 (11.0)	0.96 (0.89-1.04)[g,h]	0
	1	165 (1.0)	0.79 (0.58-1.07)[i]	NA
	1	22 (0.1)	0.99 (0.43-2,29)[j]	NA
	1	197 (1.1)	0.90 (0.62-1.32)[k]	NA
	2	2,329 (12.6)	1.03 (0.95-1.11)[a]	0
Omega 3 fatty acids[25]	31	2,628 (7.5)	0.95 (0.82-1.12)[a,l]	65
	38	390 (84.0)	0.86 (0.60-1.25)[c]	48
	25	648 (3.8)	1.03 (0.70-1.50)[m]	51
	25	565 (3.3)	0.77 (0.59-1.02)[e]	66
	26	243 (0.7)	1.17 (0.91-1.51)[f]	0
	20	54 (0.7)	**0.51 (0.31-0.85)[n]**	0
	17	11 (1.0)	0.26 (0.07-1.06)[o]	0
	37	416 (2.2)	0.85 (0.49-1.48)[p]	72
Advice to reduce dietary salt[19]	2	92 (12.3)	0.82 (0,56-1,21)[l,q]	0
Mediterranean dietary pattern[21]	1	–	HR=0.96 (0.89-1.03)[a,r]	NA
			HR=0.91 (0.8-1.04)[m,r]	NA
			HR=0.91 (0.82-1.01)[d,r]	NA
			HR=1.04 (0.90-1.19)[i,r]	NA
Qigong[29]	1	80 (26.1)	**0.56 (0.38-0.83)[f]**	NA
Health promotion interventions[27]	1	6 (2.6)	0,57 (0.11-3.07)	NA
Digital Health Interventions[33]	2	42 (4.0)	1,21 (0.58-2.58)[a]	15
Multiple risk factor interventions[11]	9	10,071 (8.3)	**0.84 (0.73-0.98)[a,h]**	82

*: number of included studies providing information of interest; RR: relative risk; I² : Higgins' heterogeneity; HR: hazard ratio; [a]: all cardiovascular events (fatal and non-fatal); NI: not informed; NA: not applicable; [b]: data from the clinical trial Physicians Health Study II (men aged ≥50); [c]: myocardial infarction; [d]: revascularization; [e]: angina; [f]: stroke; [g]: non-fatal cardiovascular disease; [h]: fixed-effect model analysis; [i]: non-fatal stroke; [j]: hemorrhagic stroke; [k]: ischemic stroke; [l]: random effects model analysis; [m]: non-fatal myocardial infarction; [n]: heart failure; [o]: peripheral vascular events; [p]: sudden death; [q]: cardiovascular morbidity; [r]: data from RCT WHI study (postmenopausal women). Parameters in bold are statistically significant.

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ed. Nonetheless, in most reviews authors called for caution in extrapolating results, as a high risk of bias in some of the RCTs was noted due to participants at varying levels of risk, different intensities interventions, lack of statistical power and insufficient length of follow-up.

Conducting RCTs in primary prevention can be challenging, and perhaps this explains scarcity of interventions and show evidence of benefit on CVD outcomes. The studies are targeted at a general population, which includes people at low risk. The interventions generally have a behavioural element, which requires a certain degree of collaboration from participants to maintain the healthy behaviour over long periods. A long follow-up is required to provide enough statistical power for CVD outcomes. The authors of the Qigong review[29] realised that the included trials were originally designed to study outcomes over one year, but it was unclear from the RCTs whether both Qigong was continuously practiced over the whole follow up and if randomization was preserved in the analysis of the RCTs over the whole follow up. Other reviews have found more positive results on intermediate, short term outcomes such as cholesterol level and high blood pressure[13,16,17,19,22,24,26-28,30].

The effectiveness of vitamin D in reducing all-cause mortality concur with the results found by Theodoratou et al[36] who conducted an umbrella review across systematic reviews and meta-analyses of observational studies of 25-hydroxyvitamin D or 1,25-dihydroxyvitamin D concentrations in plasma, along with randomised controlled trials where the intervention was vitamin D supplementation for multiple health outcomes. The results of meta-analysis showed some insignificant risk reduction in CVD and mortality outcomes across randomised controlled trials with vitamin D supplementation, while a statistically significant risk reduction was seen in the observational studies about vitamin D concentrations in plasma.

Apart from vitamin D, no other supplements showed a benefit for cardiovascular prevention. The supplements are marketed in several countries, and many people take these pills believing that it will improve their health[37]. Nevertheless the effectiveness and safety of these products ought to be further evaluated. Antioxidant supplements may even increase the risk of overall mortality[13]. Furthermore, other meta-analyses have associated supplements with increased risk of some cancers[37].

Limitations of this review are: only reviews in English and Spanish were included, and grey literature (e.g. non peer reviewed papers in unconventional information channels) was not searched; thus, we may therefore have missed some relevant studies. The strengths are: the review was conducted over several databases, and the overall risk of bias is likely to be very low as the majority of the included reviews are from Cochrane collaboration.

A limitation of the umbrella review methodology may be that we have assessed the quality of the systematic reviews using the risk of bias tool, not the quality of the individual studies within these reviews. Furthermore, the trials included in each systematic review can be quite heterogeneous in population (the Women's Health Initiative about diet in postmenopausal women[20], or the Physicians Health Study II about vitamin C supplementation in male physicians aged 50 years or older[12]), causing that observed results may not be transferable to the general population. More research should be conducted to assess whether the effect of treatment varies according to population characteristics such as gender[38], age or social class[39]. Longer-term monitoring of patients is needed to assess CVD.

Finally, the results of this review should be carefully interpreted as most studies compare non-pharmacological interventions for primary prevention against usual care, which can include recommended pharmacological treatment in higher risk patients (e.g. statins and/or antihypertensive, etc.). This means that these trials are measuring the combined effect of non-pharmaceutical interventions alongside standard pharmacological practice, rather than considering these interventions as an alternative to pharmacology. More research

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is also recommended to evaluate combinations of different interventions.

These results inform to future guidelines and clinical practice for intervention related to primary prevention of CVD. From the list of putative interventions to improve the cardiovascular health of patients in primary prevention, four of them have been shown to be effective, with minor adverse events if any. Other non-pharmacological interventions did not achieve statistical significance for CVD prevention, but did achieve significant improvements in other intermediate outcomes, such as blood pressure and lipid levels. Hence, further research is required to establish if these interventions, alone or in combination, translate into definite long-term health benefits. Given the limited evidence to date, there is therefore a need for well-conducted RCT with higher-quality design focused on long term outcomes such as CVD, as well as intermediate and surrogate endpoints, involving a long-term monitoring of non-pharmacological interventions on primary prevention to assess their effects on CVD and mortality. The role of the healthcare professional in engaging and communicating with patients also deserves further attention.

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Appendix 1

SUMMARY OF METHODOLOGICAL QUALITY OF INCLUDED STUDIES BASED ON THE ASSESSMENT OF EACH ITEM FROM THE AMSTAR CHECKLIST BY THIS REVIEW AUTHORS

	The AMSTAR checklist										
	1	2	3	4	5	6	7	8	9	10	11
Studies reporting CVD events and/ or mortality outcomes											
Multiple risk factor interventions[11]	+	+	+	+	+	+	+	+	+	+	+
Vitamin C supplementation[12]	+	+	+	+	+	+	+	+	+	+	+
Antioxidant supplements[13]	+	+	+	+	+	+	+	+	+	+	+
Vitamin D supplementation[14]	+	+	+	+	+	+	+	+	+	+	+
Selenium supplementation[15]	+	+	+	+	+	+	+	+	+	+	+
Vitamins and minerals supplements[18]	+	+	+	+	+	+	+	+	+	Θ	+
Advice to reduce dietary salt[19]	+	+	+	+	+	+	+	+	+	Θ	+
Mediterranean dietary pattern[21]	+	+	+	+	+	+	+	+	+	+	+
Omega 3 fatty acids[25]	+	+	+	+	+	+	+	+	+	+	+
Health promotion interventions[27]	+	+	+	+	+	+	+	+	+	+	+
Qigong[29]	+	+	+	+	+	+	+	+	+	+	+
Digital health interventions[33]	+	+	+	+	+	+	+	+	+	+	+
General health checks[34]	+	+	+	+	+	+	+	+	+	Θ	+
Studies not reporting CVD events or mortality outcomes											
Co-enzyme 10[16]	+	+	+	+	+	+	+	+	NA	+	+
Vitamin K supplementation[17]	+	+	+	+	+	+	+	+	NA	+	+
Increased consumption of fruit and vegetables[20]	+	+	+	+	+	+	+	+	NA	Θ	+
Increased consumption of nuts[22]	+	+	+	+	+	+	+	+	NA	+	+
Green and black tea[23]	+	+	+	+	+	+	+	+	NA	+	+
Dietary fibre supplementation[24]	+	+	+	+	+	+	+	+	NA	+	+
Omega 6 fatty acids[26]	+	+	+	+	+	+	+	+	NA	+	+
Exercise training[28]	+	+	+	+	+	+	+	+	NA	Θ	+
Tai-Chi[30]	+	+	+	+	+	+	+	+	NA	+	+
Yoga[31]	+	+	+	+	+	+	+	+	NA	+	+
Transcendental meditation[32]	+	+	+	+	+	+	+	+	NA	+	+

1: a priori design; 2: duplicate study selection and data extraction; 3: comprehensive literature search; 4: status of publication as an inclusion criteria 5: list of studies provided (included and excluded); 6: characteristics of the included studies; 7: scientific quality of the included studies assessed; 8: scientific quality of the included studies used appropriately in formulating conclusions; 9: appropriateness of methods used to combine cardiovascular outcomes of included studies; 10: publication bias assessed; 11: conflict of interest declared; CVD: cardiovascular disease; +: yes, Θ: no; NA: not applicable