Vitamin K for the primary prevention of cardiovascular disease (Review)

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[Intervention Review]

Vitamin K for the primary prevention of cardiovascular disease

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ABSTRACT

Background

A deficiency in vitamin K has been associated with increased calcium deposition and coronary artery calcification, which may lead to cardiovascular disease.

Objectives

To determine the effectiveness of vitamin K supplementation as a single nutrient supplement for the primary prevention of cardiovascular disease.

Search methods

We searched the following electronic databases: the Cochrane Central Register of Controlled Trials (CENTRAL, Issue 8 of 12, 2014); MEDLINE (Ovid, 1946 to September week 2 2014); EMBASE Classic + EMBASE (Ovid, 1947 to September 18 2014); Science Citation Index Expanded (SCI-EXPANDED) and Conference Proceedings Citation Index, Science (CPCI-S) (both 1990 to 17 September 2014) on Web of Science (Thomson Reuters); Database of Abstracts of Reviews of Effects (DARE); Health Technology Assessment Database and Health Economics Evaluations Database (Issue 3 of 4, 2014). We searched trial registers and reference lists of reviews for further studies. We applied no language restrictions.

Selection criteria

We included randomised controlled trials of vitamin K supplementation as a single nutrient supplement, lasting at least three months, and involving healthy adults or adults at high risk of cardiovascular disease. The comparison group was no intervention or placebo. The outcomes of interest were cardiovascular disease clinical events and cardiovascular disease risk factors.

Data collection and analysis

Two review authors independently selected trials for inclusion, abstracted the data and assessed the risk of bias.

Main results

We included only one small trial (60 participants randomised) which overall was judged to be at low risk of bias. The study examined two doses of menaquinone (vitamin K2) over 3 months in healthy participants aged 40 to 65 years. The primary focus of the trial was to examine the effects of menaquinone (subtype MK7) on different matrix Gla proteins (MGP - vitamin K dependent proteins in the

vessel wall) at different doses, but the authors also reported blood pressure and lipid levels. The trial did not report on our primary outcomes (cardiovascular disease clinical events) as it was small, short term and conducted in healthy participants.

In terms of cardiovascular disease risk factors, no effects were seen for vitamin K2 on blood pressure or lipid levels, although the trial was small and findings are limited. The trial did not report any of our other secondary outcomes.

Authors' conclusions

The very limited results of this review highlight the lack of evidence currently available to determine the effectiveness of vitamin K supplementation for the primary prevention of cardiovascular disease, and demonstrate the need for further high quality trials in this area.

PLAIN LANGUAGE SUMMARY

Vitamin K supplementation to prevent cardiovascular disease

Background

Cardiovascular disease (CVD) refers to a group of conditions affecting the heart and blood vessels. CVD is a global burden and varies between regions, and this variation has been linked in part to dietary factors. Such factors are important because they can be modified to help with CVD prevention and management.This review assessed the effectiveness of vitamin K supplementation as a single supplement at reducing cardiovascular death, all-cause death, non-fatal endpoints (such as heart attacks, strokes and angina) and CVD risk factors in healthy adults and adults at high risk of CVD.

Study characteristics

We searched scientific databases for randomised controlled trials (clinical trials where people are allocated at random to one of two or more treatments) looking at the effects of vitamin K supplementation in healthy adults or those at high risk of developing CVD. We did not include people who already had CVD (e.g. heart attacks and strokes). The evidence is current to September 2014.

Key results

Only one small trial met our inclusion criteria. It included 60 participants aged 40 to 65 years. This study looked at the effects of vitamin K2 supplements on CVD risk factors (blood pressure and lipid levels) over three months in healthy participants. No differences in these risk factors were seen between the comparison groups, but this was a small study and the findings are limited. The trial did not look at fatal and non-fatal cardiovascular endpoints as it was small and short term.

The evidence is currently extremely limited and further high-quality trials are needed so that the effectiveness of vitamin K supplementation for CVD prevention can be determined.

Quality of the evidence

The only trial identified for this review was judged to be at low risk of bias (so there was less chance of arriving at the wrong conclusions because of favouritism by the participants or researchers). However the evidence is limited to one small trial and no firm conclusions can be reached at this time.

BACKGROUND

Description of the condition

Cardiovascular disease (CVD) is a group of disorders affecting the heart and blood vessels (WHO 2013). CVD includes conditions such as coronary heart disease (CHD), which is a disease of the blood vessels supplying the heart muscle, and cerebrovascular dis-

ease, a disease of the blood vessels supplying the brain (WHO 2013). CVD is the primary cause of death and disability worldwide (WHO 2013). The burden of disease will increase with an ageing population and increasing levels of obesity and sedentary lifestyles. Therefore the prevention of CVD, especially by targeting modifiable risk factors, remains a key priority for public health. Atherosclerosis is one of the main mechanisms thought to cause CVD, where the arteries become blocked by plaques or atheromas (NHS 2012a). Atherosclerosis can cause CVD when the arteries are completely clogged by a blood clot or when a narrowed artery restricts blood flow, limiting the amount of blood and oxygen reaching organs or tissue (BHF 2013). While age may naturally cause arteries to narrow and become harder, the process may be accelerated by factors such as smoking, high cholesterol, hypertension, obesity, a sedentary lifestyle and ethnicity (NHS 2012a). Dietary factors may play a vital role in CVD development and may contribute to the geographic variability in CVD morbidity and mortality (Scarborough 2011; Yusuf 2001). These factors are important to consider because they can be modified, making them one of the main targets for interventions aimed at the prevention and management of CVD.

Description of the intervention

The intervention this review examines is vitamin K supplementation as a single ingredient. Vitamin K belongs to a group of similarly structured, lipophilic, hydrophobic vitamins that are required for protein biosynthesis. It occurs in two biologically-active forms. The first is phylloquinone (vitamin K1), which is mainly found in leafy green vegetables such as spinach, broccoli and cabbage. The second is menaquinone (vitamin K2), which is found in dairy products, meat and eggs (Schurgers 2000). In the western diet, phylloquinone is the most predominant form of vitamin K while menaquinone is more commonly consumed in non-western diets (Erkkila 2008; Shea 2012). In the United States (US), the current recommended daily allowance (RDA) of vitamin K is 90 μg/day for adult women and 120 μg/day for adult men (based on median intakes according to the National Health and Nutrition Examination Survey (NHANES) (1988 to 1994)) (Food and Nutrition Board 2001), while in the United Kingdom (UK), 1 µg/kg body weight/day is recommended (Department of Health 1991). For most people, vitamin K supplementation is safe and has no side effects. In the UK, the Department for Health suggests that taking 1 mg or less of vitamin K supplements a day is unlikely to cause any harm (NHS 2012b).

One function of vitamin K is as a co-factor for the gamma-glutamyl carboxylase enzyme. In certain proteins, this catalyses the carboxylation of glutamate residues to gamma-carboxyglutamyl acid residues (Gla) (Erkkila 2008; Furie 1999). Once carboxylated these Gla proteins play a role in several physiological processes such as blood coagulation, cell growth, bone formation, soft-tissue calcification and apoptosis (Erkkila 2008). Some vitamin K-dependent proteins (VKDPs) are: matrix Gla protein (MGP), a protein present in the vascular wall; growth arrest specific gene (Gas-6); coagulant factors II, VII, X and IX; and osteocalcin (Danziger 2008; Uotila 1990).

How the intervention might work

Whilst there is abundant evidence that vitamin K plays a vital role in blood coagulation, more recently there is evidence to suggest that VKDPs are important in the regulation of tissue calcification, which has implications for healthy bones and arterial vessel walls (Cranenburg 2007). Vascular vitamin K deficiency may lead to increased calcium deposition, coronary artery calcification and eventually CVD (Furie 1999; Sponk 2001). Indeed, there is evidence from observational studies that shows an association between a lack of vitamin K intake and vascular calcification (Beulens 2009; Jie 1995; Shea 2009). Observational studies have also shown that high dietary vitamin K2 (menaquinone) intake is associated with reduced risk of CVD (Gast 2009; Geleijnse 2004). The associations of the various subtypes of vitamin K2 (MK-4 to MK-9) with the risk of CVD have been examined in one study, in which the authors found the protective effect of vitamin K2 appeared to be mainly due to its subtypes MK-7, MK-8 and MK-9 (Gast 2009). This protective effect on CVD risk has not been shown for vitamin K1 (phylloquinone) in four cohort studies (Erkkila 2005; Erkkila 2007; Gast 2009; Geleijnse 2004). Notably, in the Nurses' Health Study (Erkkila 2005) the intake of vitamin K1 was associated with a lower risk of CHD, but these associations were no longer significant when dietary and lifestyle factors thought to affect CHD risk were adjusted for in the analysis, suggesting that vitamin K1 intake may be a surrogate marker for a healthy diet rather than an independent risk factor for CHD. However, in a recent analysis of data from the National Health and Nutrition Examination Surveys 2007-2008 and 2009-2010, of adults aged 50 years and older (N = 5296), inadequate vitamin K1 intake was shown to be an independent predictor of high arterial pulse pressure (Vaccaro 2013). The association between the dietary intake of different types of vitamin K and mortality has been examined in a prospective cohort analysis conducted in 7216 participants from the PREDIMED (Prevencion con Dieta Mediterranea) study (Juanola-Falgarona 2014). Vitamin K1 intake was inversely associated with a significantly reduced risk of all-cause mortality after controlling for potential confounders (hazard ratio (HR) 0.64; 95% CI 0.45 to 0.90), and individuals who increased their intake of vitamin K1 or vitamin K2 during five years of follow-up had a lower risk of all-cause mortality (HR 0.57; 95% CI 0.44 to 0.73; and HR 0.55; 95% CI 0.42 to 0.73, respectively) than individuals who decreased or did not change their intake. The authors concluded that an increase in dietary intake of vitamin K is associated with a reduced risk of all-cause mortality in a Mediterranean population at high CVD risk (Juanola-Falgarona 2014).

Vitamin K has also been associated with insulin resistance (Yoshida 2008a). The Framingham offspring cohort found that greater insulin sensitivity and better glycaemic status were associated with higher supplemental and dietary vitamin K consumption (Yoshida 2008a). Furthermore, a trial of vitamin K found that daily supplementation of 500 mg of phylloquinone for three years had a protective effect on the progression of insulin resistance in older men. However, this protective effect was not found for women (Yoshida 2008b). The biological mechanisms by which vitamin K influences insulin and glucose metabolism are not known, but vitamin K has been found in organs, for example the liver and pancreas, that are important for glucose and insulin metabolism (Stenberg 2001; Thijssen 1996).

A previous systematic review has examined the effectiveness of vitamin K1 and K2 on CHD incidence, type 2 diabetes and the metabolic syndrome (Rees 2010). Few studies - four cohort studies and one trial - met the inclusion criteria. No effects were seen for vitamin K1 on CHD, stroke or type 2 diabetes, but higher vitamin K2 intake was associated with fewer CHD events in two cohort studies. The review was limited by the small number of included studies, their design (most were observational and open to bias and confounding), and the assessment of vitamin K status by food frequency questionnaires rather than more objective measures.

Why it is important to do this review

Current evidence for the effectiveness of vitamin K supplementation for the primary prevention of CVD is limited to mainly observational studies which are open to bias and confounding (Rees 2010). There is a need to update current evidence and in particular to examine evidence from randomised controlled trials (RCTs) of vitamin K supplementation. The current review is important as it will update the trial evidence and examine a wider range of outcomes including cardiovascular mortality and morbidity, CVD risk factors, adverse events, quality of life and costs.

OBJECTIVES

To determine the effectiveness of vitamin K supplementation as a single nutrient supplement for the primary prevention of cardiovascular disease.

METHODS

Criteria for considering studies for this review

Types of studies

We included parallel group randomised controlled trials (RCTs). We included studies reported as full-text, those published as abstract only, and unpublished data.

Types of participants

We included healthy adults (aged 18 years or over) from the worldwide general population and adults at moderate to high risk of CVD (e.g. hypertension, hyperlipidaemia, overweight/obese). As this review focuses on the primary prevention of CVD, we excluded people who had experienced a previous myocardial infarction (MI), stroke, revascularisation procedure (coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA)), people with angina, and people with angiographically-defined CHD.

Types of interventions

We included RCTs comparing vitamin K supplementation as a single supplement with no intervention or placebo. We considered both vitamin K1 and vitamin K2. We excluded multi-vitamin and mineral preparations that include vitamin K since it is not possible to disentangle the specific effects of vitamin K from those of the other micronutrients.

We focused on follow-up periods of three months or more, as these are the most relevant for public health interventions. Follow-up is seen as the time elapsed since the start of the intervention and, as such, we excluded any trials with an intervention period of less than three months.

Types of outcome measures

Primary outcomes

1. Cardiovascular mortality.
2. All-cause mortality.
3. Non-fatal endpoints such as MI, hospitalisation due to coronary revascularisation (CABG or PTCA), unstable angina and any type of stroke.

Secondary outcomes

1. Changes in blood pressure (systolic and diastolic blood pressure) and blood lipids (total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides).
2. Incidence of type 2 diabetes.
3. Health-related quality of life.
4. Adverse effects (as defined by the authors of the included trials).
5. Costs.

Search methods for identification of studies

Electronic searches

We searched the following databases in *The Cochrane Library*:

- Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 8 of 12, 2014);
- Database of Abstracts of Reviews of Effects (DARE) (Issue 3 of 4, 2014);
- NHS Economic Evaluation Database (NEED) (Issue 3 of 4, 2014);
- NHS Centre for Reviews and Dissemination (CRD) database: Health Technology Assessment (HTA) (Issue 3 of 4, 2014).

We also searched:

- MEDLINE (Ovid, 1946 to September week 2, 2014);
- EMBASE Classic and EMBASE (Ovid, 1947 to 18 September 2014);
- Science Citation Index Expanded (SCI-EXPANDED), Social Sciences Citation Index (SSCI) and Conference Proceedings Citation Index - Science (CPCI-S) (both 1990 to 17 September 2014) on Web of Science (Thomson Reuters.

The search strategy for MEDLINE (Ovid) was adapted for use in the other databases (Appendix 1). We applied the Cochrane sensitivity-maximising RCT filter to MEDLINE (Ovid) and adaptations of it to the other databases, except CENTRAL (Lefebvre 2011).

We also conducted a search of ClinicalTrials.gov (www.ClinicalTrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal (apps.who.int/trialsearch/), using the search terms vitamin K AND cardio*.

We searched all databases from their inception to the present, and imposed no restriction on language of publication.

Searching other resources

We checked the reference lists of reviews and retrieved articles for additional studies. We contacted trial authors where necessary for any additional information.

Data collection and analysis

Selection of studies

Two authors (LH, CC, KR or OG) independently screened titles and abstracts for inclusion and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We retrieved the full-text study reports/publications and two authors (LH, CC, KR or OG) independently screened the full-text to identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. We resolved any disagreement through discussion or consulted a third author (NF, KR). We identified and excluded duplicates and collated multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and Characteristics of excluded studies table.

Data extraction and management

We used a data collection form for study characteristics and outcome data that was piloted on at least one study in the review. We extracted the following study characteristics:

1. Methods: study design, total duration of study, details of any 'run in' period, number of study centres and location, study setting, withdrawals and date of study.
2. Participants: number, mean age, age range, gender, inclusion criteria and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for trial, and notable conflicts of interest of trial authors.

Two authors (LH, CC) independently extracted outcome data from included studies. We resolved disagreements by consensus or by involving a third author (NF, KR). One author (LH) transferred data into Review Manager 5 (RevMan 2014). We double-checked that data were entered correctly by comparing the data presented in the systematic review with the study reports.

Assessment of risk of bias in included studies

Two authors (LH, CC) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by discussion or by involving another author (NF, KR). We assessed the risk of bias according to the following domains:

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias (e.g. industry funding).

We graded each potential source of bias as high, low or unclear risk, and provided a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We summarised the 'Risk of bias' judgements for each of the domains

listed. Where information on risk of bias relates to unpublished data or correspondence with a trialist, we noted this in the 'Risk of bias' table.
When considering treatment effects, we took into account the risk of bias for the studies that contributed to that outcome.

Assessment of bias in conducting the systematic review

We conducted the review according to the published protocol (Hartley 2014) and report any deviations from it in the Differences between protocol and review section of the systematic review.

Measures of treatment effect

We analysed dichotomous data as odds ratios or risk ratios with 95% confidence intervals and continuous data as mean difference or standardised mean difference with 95% confidence intervals. We entered data presented as a scale with a consistent direction of effect.
Where applicable we intended to describe skewed data reported as medians and interquartile ranges narratively within the results text.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity. If we identified substantial heterogeneity (greater than 50%) we reported it and explored possible causes by prespecified subgroup analysis.

Assessment of reporting biases

If we were able to pool more than 10 trials, we would have created and examined a funnel plot to explore possible small study biases for the primary outcomes. However, there were insufficient trials included for these analyses.

Data synthesis

We conducted statistical analysis using Review Manager 5 (RevMan 2014). We entered continuous data as means and standard deviations. In the absence of substantial heterogeneity (greater than 50%) we combined the results using a fixed-effect model. For trials with more than one intervention arm, we divided the control group by the number of intervention arms to weight the studies appropriately.

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses, but there were insufficient trials included for these analyses:

1. Subgroups of vitamin K (vitamin K1 and vitamin K2).
2. Baseline risk of participants (healthy and high risk of CVD).
3. Vitamin K dosage.

We intended to use the formal test for subgroup interactions in Review Manager 5 (RevMan 2014).

Sensitivity analysis

We planned to carry out the following sensitivity analyses, but there were insufficient trials included for these analyses:

1. Only including studies with a low risk of bias.
2. Only including studies with a follow-up period of six months.

Reaching conclusions

We based our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We avoided making recommendations for practice and our implications for research suggest priorities for future research and outline what the remaining uncertainties are in the area.

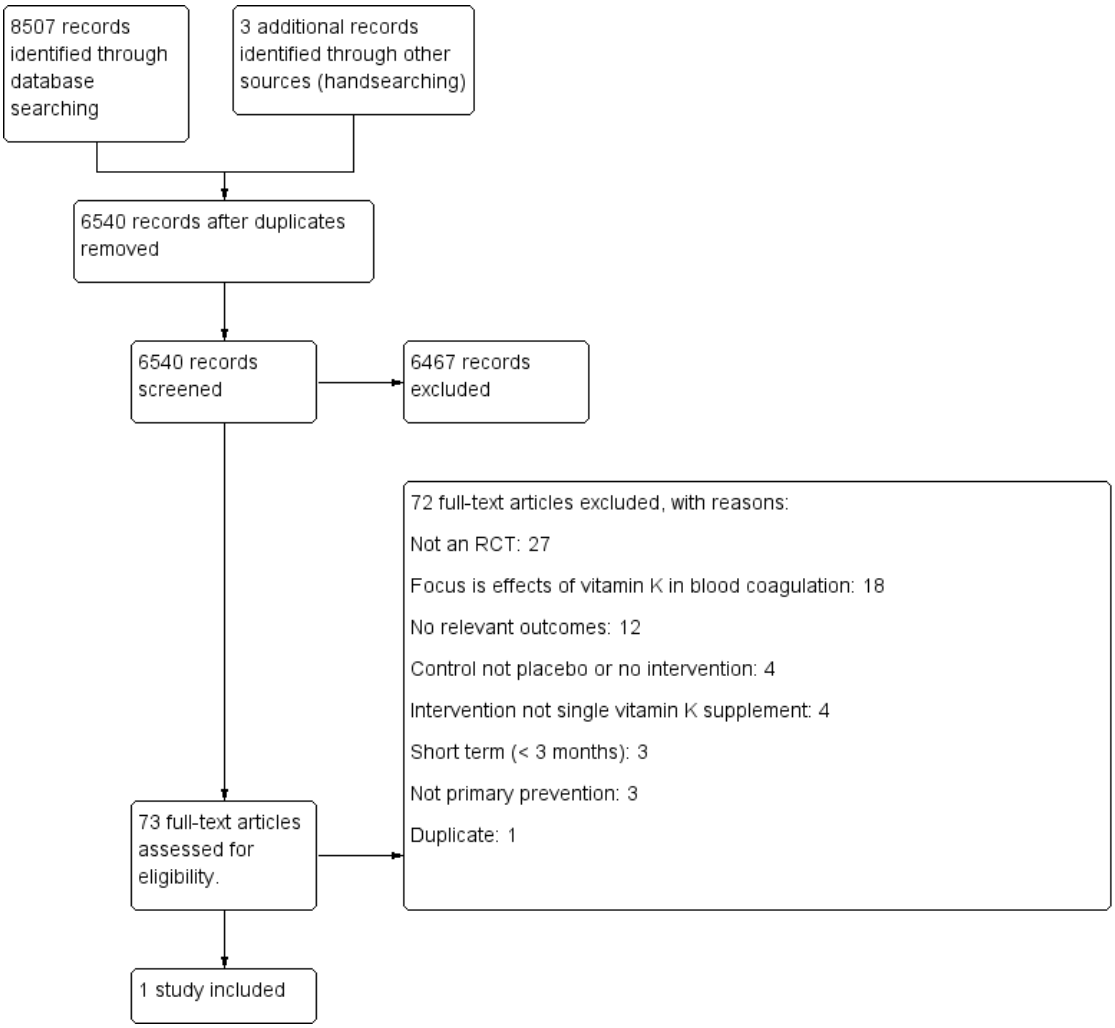
RESULTS

Description of studies

Results of the search

The searches generated 8507 hits and 6540 records after de-duplication. Screening the titles and abstracts identified 73 papers for formal assessment of inclusion and exclusion. Of these, only one trial met the inclusion criteria. Details of the flow of studies through the review can be seen in Figure 1.

Figure 1. Study flow diagram.



Included studies

Details of the included study are provided in the Characteristics of included studies table. Sixty apparently healthy men and women who were 40 to 65 years old with a body mass index (BMI) of between 18.5 and 30 were recruited in the Netherlands and randomised to three arms - 180μg/d or 360μg/d of menaquinone (vitamin K2 subtype MK-7) or to a placebo group (Dalmeijer 2012). The intervention period was three months. The focus of the study was to examine the effects of menaquinone-7 supplementation on different matrix Gla proteins (MGP - vitamin K dependent proteins in the vessel wall) at different doses, but outcomes also included blood pressure and lipid levels (Dalmeijer 2012).

Excluded studies

Details and reasons for exclusion of the studies that most closely miss our strict inclusion criteria are provided in the Characteristics of excluded studies table. Reasons for exclusion for the majority of studies included alternative designs (not RCTs), use of vitamin K in blood coagulation, and no relevant outcomes (or intermediate CVD outcomes) (see Figure 1).

Risk of bias in included studies

Details are presented for the included trial in the 'Risk of bias' table in the Characteristics of included studies table.

Allocation

The method of random sequence generation was stated and judged to be of low risk of bias, while the method of allocation concealment was unclear (Dalmeijer 2012).

Blinding

The included trial used a placebo and the authors state the trial was double blind, therefore there was low risk of performance bias. The authors did not explicitly state that outcome assessors were blind to group allocation so this was judged to be unclear (Dalmeijer 2012).

Incomplete outcome data

The study reported losses to follow-up and provided details for these and so this study was judged to be at low risk of attrition bias (Dalmeijer 2012).

Selective reporting

Risk of bias for selective reporting was judged to be low, as the authors clearly stated primary and secondary outcomes and reported the results of these (Dalmeijer 2012).

Other potential sources of bias

The risk of bias from other potential sources was judged to be low as adherence to treatment was 96%, baseline characteristics were well balanced and the trial was not commercially funded (Dalmeijer 2012).

Effects of interventions

Cardiovascular events

Cardiovascular and all-cause mortality

The included study was short term and hence did not report clinical outcomes (Dalmeijer 2012).

Non-fatal clinical events

The included study was short term and hence did not report clinical outcomes (Dalmeijer 2012)

Cardiovascular risk factors

Blood pressure

The included study examined the effect of 180μg/d or 360μg/d of menaquinone-7 (vitamin K2 subtype MK-7) on blood pressure. The results were analysed independently by each dose and then combined in a meta-analysis. The paper did not present data in a usable format, so we contacted the authors who provided the relevant information (Dalmeijer 2012).

There was no significant heterogeneity between the two intervention arms so results were pooled using a fixed-effect model. There were no statistically significant effects of MK-7 on either systolic blood pressure (SBP) (mean difference -2.74 mm/Hg; 95% confidence interval (CI) -11.49 to 6.02) Analysis 1.1 or diastolic blood pressure (DBP) (mean difference 1.09 mm/Hg; 95% CI -4.25 to 6.43) Analysis 1.2.

Lipid levels

The included study examined the effect of 180μg/d or 360μg/d of menaquinone-7 (vitamin K2 subtype MK-7) on lipid levels. The results were analysed independently by each dose and then combined in a meta-analysis. The paper did not present data in a usable format, so we contacted the authors who provided the relevant information (Dalmeijer 2012).

There was no significant heterogeneity between the two intervention arms so results were pooled using a fixed-effect model. There were no statistically significant effects of MK-7 on either total cholesterol (mean difference 0.1 mmol/L; 95% CI -0.37 to 0.57) Analysis 2.1, LDL cholesterol (mean difference 0.1 mmol/L; 95% CI -0.37 to 0.56) Analysis 2.2, HDL cholesterol (mean difference 0 mmol/L; 95% CI -0.27 to 0.27) Analysis 2.3 or triglycerides (mean difference 0.1 mmol/L; 95% CI -0.1 to 0.3) Analysis 2.4.

Occurrence of type 2 diabetes

The included study did not report the occurrence of type 2 diabetes.

Health-related quality of life

The included study did not report health-related quality of life.

Adverse effects

The included study did not report adverse effects.

Costs

The included study did not report costs.

DISCUSSION

Summary of main results

Of the 6540 papers screened, we included only one small study (60 participants randomised) with a duration of three months. Additional data were requested and received for blood pressure and lipid levels, as these were not provided in a useable format for analysis in the original publication.

As this study was short term and conducted in healthy participants, it did not report our primary outcomes, cardiovascular disease (CVD) clinical events. The included study reported CVD risk factors where no effects were seen for vitamin K2 on blood pressure or lipid levels, although the trial was small and findings are limited. The trial did not report any of our other secondary outcomes.

The very limited results of this review highlight the lack of evidence for vitamin K supplementation for the primary prevention of CVD.

Overall completeness and applicability of evidence

Only one small study met our inclusion criteria so the results are extremely limited (Dalmeijer 2012). This trial recruited healthy male and female participants aged 40 to 65 years from the Netherlands. Participants were randomised to two doses of vitamin K2, and reported only on CVD risk factors, where no effects were seen for the intervention versus placebo, or between doses, but the numbers were extremely small and no firm conclusions can be drawn.

If there were sufficient trials in this review it was our intention to stratify results according to vitamin K subgroups, baseline risk and vitamin K dosage.

Our strict inclusion criteria meant that we excluded three potentially-relevant studies to examine the effects of vitamin K for the primary prevention of CVD. Two ongoing trials were excluded on the basis of not reporting outcomes relevant to this review (van Varik; Vermeer). These authors are measuring intermediate CVD outcomes, coronary artery calcification score and arterial stiffness (van Varik), vascular thickness and elasticity (Vermeer). A completed trial was excluded as the comparison group was not no intervention or placebo, but rather a multivitamin preparation that the intervention group received as well in addition to 500µg per day of vitamin K1 (Shea 2009). Further details and results of this trial are provided in the section Agreements and disagreements with other studies or reviews below.

Quality of the evidence

Only one study met the inclusion criteria for this review. Overall this was judged to be at low risk of bias. Small study bias is a concern with studies recruiting small numbers of participants (Nüesch 2010; Sterne 2000; Sterne 2001). Due to the lack of included studies we were unable to examine the effects of publication bias in funnel plots.

Potential biases in the review process

A comprehensive search across major databases for interventions involving vitamin K supplementation was carried out for this review. In addition, the reference lists of systematic reviews were screened and authors contacted for information when needed. All screening, inclusion and exclusion and data abstraction were carried out independently by two review authors.

Multivitamins and mineral preparations including vitamin K were excluded from this review because it would not be possible to disentangle the specific effects of vitamin K. This did, however, limit the number of trials that were eligible for inclusion. Our strict inclusion criteria for the comparison group (placebo or no intervention) also led to the exclusion of one trial that was potentially contributory (Shea 2009) as discussed above. Two ongoing trials reporting intermediate CVD outcomes were also excluded as they did not report any of our primary or secondary outcomes (van Varik; Vermeer).

The results of this review are currently based on one small trial (Dalmeijer 2012) and are therefore extremely limited.

Agreements and disagreements with other studies or reviews

To our knowledge, no other systematic review including only RCTs has been conducted specifically to examine the effects of vitamin K supplementation in adults for the primary prevention of CVD. A previous systematic review which included evidence from observational studies examined the effect of vitamin K intake on cardio-metabolic outcomes (Rees 2010). No associations were found between vitamin K1 intake and coronary heart disease (CHD) in the four cohort studies reporting this, or stroke in two cohorts. Increased vitamin K2 intake was, however, associated with fewer CHD events in two cohort studies reporting this (Rees 2010). Only one trial and four cohort studies were included in this review. A secondary analysis of the trial reported the prevalence of type 2 diabetes at baseline and after three years of follow-up where no effects of vitamin K1 supplementation were found (Shea 2009).

The clinical trial reported in this previous review (Rees 2010) did not meet the inclusion criteria for the current review. It was excluded from the current review as the comparison group was a multivitamin preparation and not a placebo or no intervention (Shea 2009). The intervention group received the same multivitamin in addition to 500µg per day vitamin K1 supplementation. The trial was designed to look at the effects of vitamin K1 supple-

mentation on bone mineral density and coronary artery calcium scores in 388 men and women aged 60 to 81 years over 3 years of follow-up, and was conducted in the USA (Shea 2009). In an intention-to-treat analysis there was no difference in the coronary artery calcium scores between the intervention and control groups. There was no difference between the intervention and control groups in the incidence of CVD events which the study defined as CHD, myocardial infarction (MI), stroke, angioplasty, angina, atrial fibrillation or heart failure. In terms of CVD risk factors, no statistically significant effects were seen with vitamin K1 on blood pressure or lipid levels (Shea 2009). This study was judged to be at low risk of bias for performance, detection, attrition and reporting bias, and at unclear risk of selection bias (Shea 2009).

No direct comparisons can be made between this trial (Shea 2009) and the trial included in the review (Dalmeijer 2012) as they examined the effects of different forms of vitamin K, in different age groups, and over different time periods.

AUTHORS' CONCLUSIONS

Implications for practice

Only one trial randomising 60 participants met the inclusion criteria for this review (Dalmeijer 2012). Given the extremely limited evidence to date, this review cannot make any definitive conclusions about the effects of vitamin K supplementation for the primary prevention of CVD.

Implications for research

There is a complete lack of randomised controlled trials looking at the effects of vitamin K supplementation for the primary prevention of CVD. In particular, there is a shortage of well-conducted randomised controlled trials examining the effects of vitamin K over the long term to determine the effects of such interventions on CVD events and CVD risk factors. These trials are needed to determine the effects of vitamin K in CVD prevention. We also found no trials reporting economic evaluations of vitamin K supplementation, adverse events or health-related quality of life.

ACKNOWLEDGEMENTS

We are grateful to Nicole Martin for conducting the searches for this review. We are also grateful to Dr Booth and Dr Dalmeijer for providing extra information about their trials (Dalmeijer 2012; Shea 2009).

REFERENCES

References to studies included in this review

Dalmeijer 2012 *{published data only}*
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Dalmeijer 2012 180μg *{published data only}*
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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Dalmeijer 2012

Methods	RCT involving vitamin K2
Participants	Sixty one apparently healthy men and women who were 40 to 65 years old with a BMI between 18.5 and 30 were recruited and randomised to three arms - 180μg/d or 360μg/d of MK-7 or to the control group who received a placebo. Twenty-two participants were randomised to 180μg/d of MK-7, 19 were allocated to 360μg/d of MK-7 and 20 were randomised to the control group. One participant withdrew during the run in period leaving 18 allocated to the 360μg/d of MK-7 group, with 60 overall analysed Exclusion criteria: using vitamin K antagonists, using chronic medication for cardiovascular diseases, using menopausal hormone therapy, having a known history with coagulation problems, smoking, habitual vitamin K2 intake >90μg/d, vegans and known soy allergy
Interventions	180μg/d: MK-7 capsule containing 180μg of MK-7 and linseed oil. Source of MK-7 was MenaQ7. Received one MK-7 capsule and 1 placebo capsule each day 360μg/day: 2 MK-7 capsules containing 180μg of MK-7 and linseed oil. Source of MK-7 was MenaQ7. Received 2 MK-7 capsules daily Placebo: Similar in taste and appearance to MK-7 capsule. Received two placebo capsules daily. Placebo tablets contained 210mg of linseed oil The participants were told to take the capsules with the evening meal and were asked to maintain their habitual food consumption, body weight and physical activity pattern Follow-up: 12 weeks
Outcomes	Blood pressure and lipid levels
Notes	Authors were contacted for extra information on blood pressure and lipid levels for each point at which these were measured. Authors responded with the requested information

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Through a web-based application
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	A placebo used and the authors state that the trial was double blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated

Dalmeijer 2012 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No ITT analysis but details of loss to follow-up were provided and loss to follow-up was low (only one person withdrew)
Selective reporting (reporting bias)	Low risk	All outcomes stated were reported
Other bias	Low risk	Baseline characteristics were well balanced, adherence was good (96%) and the trial was not commercially funded

Dalmeijer 2012 180μg

Methods	See details from above study. This arm of the trial examines 180μg of MK-7/day
Participants	
Interventions	
Outcomes	
Notes	

Dalmeijer 2012 360μg

Methods	See details from above study.This arm of the trial examines 360μg of MK-7/day
Participants	
Interventions	
Outcomes	
Notes	

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Braam 2004	Vitamin K administered as part of a multivitamin preparation
Emaus 2010	No relevant outcomes
Kristensen 2008	Short term (6 weeks)
Kumar 2010	No relevant outcomes

(*Continued*)

Kurnatowska 2013	Intermediate outcomes (coronary artery calcification score (CACS) and common carotid intima media thickness (CCA-IMT) in chronic kidney disease patients
Shea 2009	Comparison group not placebo or no intervention
van Varik	Ongoing trial reporting intermediate outcomes (CACS, arterial stiffness)
Vermeer	Ongoing trial reporting intermediate outcomes (vascular thickness and elasticity)

DATA AND ANALYSES

Comparison 1. Blood pressure

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Systolic blood pressure, change from baseline (mmHg).	2	60	Mean Difference (IV, Fixed, 95% CI)	-2.74 [-11.49, 6.02]
2 Diastolic blood pressure, change from baseline (mmHg).	2	60	Mean Difference (IV, Fixed, 95% CI)	1.09 [-4.25, 6.43]

Comparison 2. Lipid levels

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total cholesterol, change from baseline (mmol/l).	2	60	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.37, 0.57]
2 LDL-C, change from baseline (mmol/l).	2	60	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.37, 0.56]
3 HDL-C, change from baseline (mmol/l).	2	60	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.27, 0.27]
4 Triglycerides, change from baseline (mmol/l).	2	60	Mean Difference (IV, Fixed, 95% CI)	0.1 [-0.10, 0.30]

Analysis 1.1. Comparison 1 Blood pressure, Outcome 1 Systolic blood pressure, change from baseline (mmHg)..

Review: Vitamin K for the primary prevention of cardiovascular disease

Comparison: 1 Blood pressure

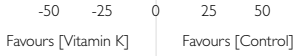
Outcome: 1 Systolic blood pressure, change from baseline (mmHg).

Study or subgroup	Vitamin K N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Dalmeijer 2012 180µ g	22	-0.87 (16.4)	10	5.88 (16)		52.7 %	-6.75 [-18.80, 5.30]
Dalmeijer 2012 360µ g	18	7.62 (17.3)	10	5.88 (16)		47.3 %	1.74 [-11.00, 14.48]
Total (95% CI)	**40**		**20**			**100.0 %**	**-2.74 [-11.49, 6.02]**

Heterogeneity: Chi^2 = 0.90, df = 1 (P = 0.34); I^2 =0.0%

Test for overall effect: Z = 0.61 (P = 0.54)

Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1 Blood pressure, Outcome 2 Diastolic blood pressure, change from baseline (mmHg)..

Review: Vitamin K for the primary prevention of cardiovascular disease

Comparison: 1 Blood pressure

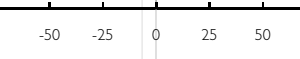
Outcome: 2 Diastolic blood pressure, change from baseline (mmHg).

Study or subgroup	Vitamin K N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Dalmeijer 2012 180µ g	22	0.82 (10.9)	10	0.82 (9.3)		52.8 %	0.0 [-7.35, 7.35]
Dalmeijer 2012 360µ g	18	3.14 (11.3)	10	0.82 (9.3)		47.2 %	2.32 [-5.46, 10.10]
Total (95% CI)	**40**		**20**			**100.0 %**	**1.09 [-4.25, 6.43]**

Heterogeneity: Chi^2 = 0.18, df = 1 (P = 0.67); I^2 =0.0%

Test for overall effect: Z = 0.40 (P = 0.69)

Test for subgroup differences: Not applicable



Analysis 2.1. Comparison 2 Lipid levels, Outcome 1 Total cholesterol, change from baseline (mmol/l)..

Review: Vitamin K for the primary prevention of cardiovascular disease

Comparison: 2 Lipid levels

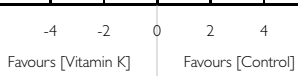
Outcome: 1 Total cholesterol, change from baseline (mmol/l).

Study or subgroup	Vitamin K N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Dalmeijer 2012 180µ g	22	0 (0.7)	10	-0.2 (0.8)		66.7 %	0.20 [-0.38, 0.78]
Dalmeijer 2012 360µ g	18	-0.3 (1.4)	10	-0.2 (0.8)		33.3 %	-0.10 [-0.91, 0.71]
Total (95% CI)	**40**		**20**			**100.0 %**	**0.10 [-0.37, 0.57]**

Heterogeneity: $Chi^2 = 0.35$, df = 1 (P = 0.56); $I^2 = 0.0\%$

Test for overall effect: Z = 0.42 (P = 0.68)

Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2 Lipid levels, Outcome 2 LDL-C, change from baseline (mmol/l)..

Review: Vitamin K for the primary prevention of cardiovascular disease

Comparison: 2 Lipid levels

Outcome: 2 LDL-C, change from baseline (mmol/l).

Study or subgroup	Vitamin K N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Dalmeijer 2012 180µ g	22	-0.1 (0.8)	10	-0.1 (0.9)		51.4 %	0.0 [-0.65, 0.65]
Dalmeijer 2012 360µ g	18	0.1 (0.8)	10	-0.1 (0.9)		48.6 %	0.20 [-0.47, 0.87]
Total (95% CI)	**40**		**20**			**100.0 %**	**0.10 [-0.37, 0.56]**

Heterogeneity: $Chi^2 = 0.18$, df = 1 (P = 0.67); $I^2 = 0.0\%$

Test for overall effect: Z = 0.41 (P = 0.68)

Test for subgroup differences: Not applicable

Analysis 2.3. Comparison 2 Lipid levels, Outcome 3 HDL-C, change from baseline (mmol/l)..

Review: Vitamin K for the primary prevention of cardiovascular disease

Comparison: 2 Lipid levels

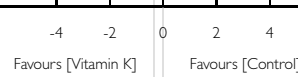
Outcome: 3 HDL-C, change from baseline (mmol/l).

Study or subgroup	Vitamin K N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Dalmeijer 2012 180µ g	22	0 (0.5)	10	0 (0.5)		51.7 %	0.0 [-0.37, 0.37]
Dalmeijer 2012 360µ g	18	0 (0.5)	10	0 (0.5)		48.3 %	0.0 [-0.39, 0.39]
Total (95% CI)	**40**		**20**			**100.0 %**	**0.0 [-0.27, 0.27]**

Heterogeneity: $Chi^2 = 0.0$, df = 1 (P = 1.00); $I^2 = 0.0\%$

Test for overall effect: Z = 0.0 (P = 1.0)

Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2 Lipid levels, Outcome 4 Triglycerides, change from baseline (mmol/l)..

Review: Vitamin K for the primary prevention of cardiovascular disease

Comparison: 2 Lipid levels

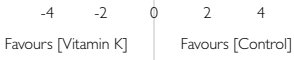
Outcome: 4 Triglycerides, change from baseline (mmol/l).

Study or subgroup	Vitamin K N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Dalmeijer 2012 180µ g	22	0 (0.36)	10	-0.1 (0.4)		49.0 %	0.10 [-0.19, 0.39]
Dalmeijer 2012 360µ g	18	0 (0.3)	10	-0.1 (0.4)		51.0 %	0.10 [-0.18, 0.38]
Total (95% CI)	**40**		**20**			**100.0 %**	**0.10 [-0.10, 0.30]**

Heterogeneity: Chi^2 = 0.0, df = 1 (P = 1.00); I^2 =0.0%

Test for overall effect: Z = 0.97 (P = 0.33)

Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. MEDLINE (OVID) search strategy

Cochrane Library

#1 MeSH descriptor: [Vitamin K] explode all trees
#2 vitamin* near/4 k*
#3 green near/2 vegetable*
#4 phytomenadione
#5 phytonadione
#6 konakion
#7 phylloquinone
#8 Phylloquinine
#9 phyllohydroquinone
#10 aquamephyton

#11 menaquinone*
#12 menadione
#13 vi?asol
#14 2-methyl-14-naphthoquinone
#15 2-methylnaphthoquinone
#16 2-methyl-14-naphthalenedione
#17 acetomenaphthone
#18 farnoquinone
#19 menadiol
#20 menatetrenone
#21 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20
#22MeSH descriptor: [Cardiovascular Diseases] explode all trees
#23 cardio*
#24 cardia*
#25 heart*
#26 coronary*
#27 angina*
#28 ventric*
#29 myocard*
#30 pericard*
#31 isch?em*
#32 emboli*
#33 arrhythmi*
#34 thrombo*
#35 atrial next fibrillat*
#36 tachycardi*
#37 endocardi*
#38 (sick next sinus)
#39 MeSH descriptor: [Stroke] explode all trees
#40 (stroke or stokes)
#41 cerebrovasc*
#42 cerebral next vascular
#43 apoplexy
#44 (brain near/2 accident*)
#45 ((brain* or cerebral or lacunar) near/2 infarct*)
#46 MeSH descriptor: [Hypertension] explode all trees
#47 hypertensi*
#48 (peripheral next arter* next disease*)
#49 ((high or increased or elevated) near/2 blood pressure)
#50 MeSH descriptor: [Hyperlipidemias] explode all trees
#51 hyperlipid*
#52 hyperlip?emia*
#53 hypercholesterol*
#54 hypercholester?emia*
#55 hyperlipoprotein?emia*
#56 hypertriglycerid?emia*
#57 MeSH descriptor: [Arteriosclerosis] explode all trees
#58 MeSH descriptor: [Cholesterol] explode all trees
#59 cholesterol
#60 “coronary risk factor*”
#61 MeSH descriptor: [Blood Pressure] this term only
#62 “blood pressure”

#63 #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62
#64#21 and #63

MEDLINE Ovid

1. exp Vitamin K/
2. (vit* adj6 k*).tw.
3. (green adj2 vegetable*).tw.
4. phytomenadione.tw.
5. phytonadione.tw.
6. konakion.tw.
7. phylloquinone.tw.
8. Phylloquinine.tw.
9. phyllohydroquinone.tw.
10. aquamephyton.tw.
11. menaquinone*.tw.
12. menadione.tw.
13. vi?asol.tw.
14. 2-methyl-14-naphthoquinone.tw.
15. 2-methylnaphthoquinone.tw.
16. 2-methyl-14-naphthalenedione.tw.
17. acetomenaphthone.tw.
18. farnoquinone.tw.
19. menadiol.tw.
20. menatetrenone.tw.
21. or/1-20
22. exp Cardiovascular Diseases/
23. cardio*.tw.
24. cardia*.tw.
25. heart*.tw.
26. coronary*.tw.
27. angina*.tw.
28. ventric*.tw.
29. myocard*.tw.
30. pericard*.tw.
31. isch?em*.tw.
32. emboli*.tw.
33. arrhythmi*.tw.
34. thrombo*.tw.
35. atrial fibrillat*.tw.
36. tachycardi*.tw.
37. endocardi*.tw.
38. (sick adj sinus).tw.
39. exp Stroke/
40. (stroke or stokes).tw.
41. cerebrovasc*.tw.
42. cerebral vascular.tw.
43. apoplexy.tw.
44. (brain adj2 accident*).tw.
45. ((brain* or cerebral or lacunar) adj2 infarct*).tw.
46. exp Hypertension/

47. hypertensi*.tw.
48. peripheral arter* disease*.tw.
49. ((high or increased or elevated) adj2 blood pressure).tw.
50. exp Hyperlipidemias/
51. hyperlipid*.tw.
52. hyperlip?emia*.tw.
53. hypercholesterol*.tw.
54. hypercholester?emia*.tw.
55. hyperlipoprotein?emia*.tw.
56. hypertriglycerid?emia*.tw.
57. exp Arteriosclerosis/
58. exp Cholesterol/
59. cholesterol.tw.
60. "coronary risk factor* ".tw.
61. Blood Pressure/
62. blood pressure.tw.
63. or/22-62
64. 21 and 63
65. randomized controlled trial.pt.
66. controlled clinical trial.pt.
67. randomized.ab.
68. placebo.ab.
69. drug therapy.fs.
70. randomly.ab.
71. trial.ab.
72. groups.ab.
73. 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72
74. exp animals/ not humans.sh.
75. 73 not 74
76. 64 and 75

EMBASE (Ovid)

1. exp vitamin K group/
2. (vit* adj6 k*).tw.
3. (green adj2 vegetable*).tw.
4. phytomenadione.tw.
5. phytonadione.tw.
6. konakion.tw.
7. phylloquinone.tw.
8. Phylloquinine.tw.
9. phyllohydroquinone.tw.
10. aquamephyton.tw.
11. menaquinone*.tw.
12. menadione.tw.
13. vi?asol.tw.
14. 2-methyl-14-naphthoquinone.tw.
15. 2-methylnaphthoquinone.tw.
16. 2-methyl-14-naphthalenedione.tw.
17. acetomenaphthone.tw.
18. farnoquinone.tw.
19. menadiol.tw.
20. menatetrenone.tw.

21. or/1-20
22. exp cardiovascular disease/
23. cardio*.tw.
24. cardia*.tw.
25. heart*.tw.
26. coronary*.tw.
27. angina*.tw.
28. ventric*.tw.
29. myocard*.tw.
30. pericard*.tw.
31. isch?em*.tw.
32. emboli*.tw.
33. arrhythmi*.tw.
34. thrombo*.tw.
35. atrial fibrillat*.tw.
36. tachycardi*.tw.
37. endocardi*.tw.
38. (sick adj sinus).tw.
39. exp cerebrovascular disease/
40. (stroke or stokes).tw.
41. cerebrovasc*.tw.
42. cerebral vascular.tw.
43. apoplexy.tw.
44. (brain adj2 accident*).tw.
45. ((brain* or cerebral or lacunar) adj2 infarct*).tw.
46. exp hypertension/
47. hypertensi*.tw.
48. peripheral arter* disease*.tw.
49. ((high or increased or elevated) adj2 blood pressure).tw.
50. exp hyperlipidemia/
51. hyperlipid*.tw.
52. hyperlip?emia*.tw.
53. hypercholesterol*.tw.
54. hypercholester?emia*.tw.
55. hyperlipoprotein?emia*.tw.
56. hypertriglycerid?emia*.tw.
57. exp Arteriosclerosis/
58. exp Cholesterol/
59. cholesterol.tw.
60. "coronary risk factor*".tw.
61. Blood Pressure/
62. blood pressure.tw.
63. or/22-62
64. 21 and 63
65. random$.tw.
66. factorial$.tw.
67. crossover$.tw.
68. cross over$.tw.
69. cross-over$.tw.
70. placebo$.tw.
71. (doubl$ adj blind$).tw.
72. (singl$ adj blind$).tw.
73. assign$.tw.

74. allocat$.tw.
75. volunteer$.tw.
76. crossover procedure/
77. double blind procedure/
78. randomized controlled trial/
79. single blind procedure/
80. 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79
81. (animal/ or nonhuman/) not human/
82. 80 not 81
83. 64 and 82
84. limit 83 to embase

Web of Science

15 #14 AND #13
14 TS=(random* or blind* or allocat* or assign* or trial* or placebo* or crossover* or cross-over*)
13 #12 AND #4
12 #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5
11 TS=(cardio* OR cardia* OR heart* OR coronary* OR angina* OR ventric* OR myocard*)
10 TS=(pericard* OR isch?em* OR emboli* OR arrhythmi* OR thrombo*)
9 TS=("atrial fibrillat*" OR tachycardi* OR endocardi*)
8 TS=(stroke OR stokes OR cerebrovasc* OR cerebral OR apoplexy OR (brain SAME accident*) OR (brain SAME infarct*))
7 TS=(hypertensi* OR "peripheral arter* disease*")
6 TS=("high blood pressure")
5 TS=(hyperlipid* OR hyperlip?emia* OR hypercholesterol* OR hypercholester?emia* OR hyperlipoprotein?emia* OR hypertriglyceri d?emia*)
4 #3 OR #2 OR #1
3 TS=(phytomenadione OR phytonadione OR konakion OR phylloquinone OR Phylloquinine OR phyllohydroquinone OR aquamephyton OR menaquinone* OR menadione OR vi?asol OR 2-methyl-14-naphthoquinone OR 2-methylnaphthoquinone OR 2-methyl-14-naphthalenedione OR acetomenaphthone OR farnoquinone OR menadiol OR menatetrenone)
2 TS=(green NEAR/2 vegetable*)
1 TS=(vit* NEAR/6 k)

CONTRIBUTIONS OF AUTHORS

All authors contributed to the protocol development (Hartley 2014). The Trials Search Co-ordinators of the Cochrane Heart Group ran the searches. LH, CC, KR and OG screened titles and abstracts and assessed studies for formal inclusion and exclusion. LH and CC abstracted data and assessed methodological rigour. LH wrote the first draft of the review and KR contributed to later drafts.

DECLARATIONS OF INTEREST

None known

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

AMED and OpenGrey were not searched due to lack of resources.

For updates: We are planning to include a 'Summary of findings' table and GRADE assessment. We will also consider a change of the inclusion criteria to allow studies where the intervention and control group received the same co-intervention.