# Supplementary data

## Supplemental Table S1

PICOS criteria for inclusion of studies

|  |  |  |
| --- | --- | --- |
| Parameter | Clinical trials | Longitudinal studies |
| Population | All adult populations (age > 18 years) | All adult populations (age > 18 years) |
| Intervention | Supplementation with vitamin K | No intervention |
| Comparison | Treatment versus control | Level of vitamin K dependent protein (continuous variable or high vs low) |
| Outcome | Vascular calcification, vascular stiffness or vitamin K dependent protein | Hazard ratio of fatal or non-fatal cardiovascular disease or mortality |
| Setting | Randomised or non-randomised controlled trial | Longitudinal studies |

## Supplemental Table S2

Meta-regression model with the mean difference (%) in a) vascular calcification and b) vascular stiffness as a dependent variable

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 1. **Impact of covariates on heterogeneity in vascular calcification studies** | | | | |
| **Variable** | **Unadjusted** | | | |
|  | **Coefficient** | **95% CI** | **P** | **Tau2** |
| **No covariate** |  | | | **0.00** |
| Year of publication | 0.25 | -6.52, 7.01 | 0.94 | 80.0 |
| Duration of follow-up | -0.72 | -2.70,1.27 | 0.48 | 23.8 |
| Vitamin K form (K1/K2) | 15.16 | -6.52, 36.84 | 0.17 | 0.00 |
| Dose | -0.01 | -0.02, 0.004 | 0.23 | 0.00 |
| Outcome | -11.74 | -32.27, 8.78 | 0.26 | 0.00 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 1. **Impact of covariates on heterogeneity in vascular stiffness studies** | | | | |
| **Variable** | **Unadjusted** | | | |
|  | **Coefficient** | **95% CI** | **P** | **Tau2** |
| **No covariate** |  | | | **6.39** |
| Year of publication | 0.55 | -0.12, 1.21 | 0.11 | 0.76 |
| Duration of follow-up | -0.18 | -0.43, 0.07 | 0.16 | 2.83 |
| Vitamin K form (K1/K2) | 5.98 | -2.28, 14.25 | 0.16 | 2.77 |
| Dose | -0.01 | -0.02, 0.001 | 0.10 | 0.63 |
| Outcome | 5.98 | -2.28, 14.25 | 0.16 | 2.77 |

## Supplemental Table S3

Cochrane risk of bias: studies included in the vitamin K intervention analysis were assessed according to the Cochrane risk of bias tool(26). Each study was allocated a score of Low, High or Unclear for each of the factors listed in the Supplemental Table below.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Year** | **Random sequence generation** | **Allocation concealment** | **Blinding of participants and personnel** | **Blinding of outcome assessment** | **Incomplete outcome reporting** | **Selective reporting** | **Other bias** |
| Binkley | 2009 | Unclear | Low | Low | Low | Unclear | Low | Low |
| Booth | 2008 | Unclear | Low | Low | Low | Low | Low | Low |
| Braam | 2004 | Low | Low | Low | Low | Low | Unclear | Low |
| Brandenburg | 2017 | Unclear | High | Unclear | Low | Low | Unclear | Low |
| Dalmeijer | 2012 | Low | Unclear | Low | Low | Low | Unclear | Low |
| Fulton | 2016 | Low | Low | Low | Low | Low | Low | Low |
| Knapen | 2015 | Unclear | Low | Low | Low | Low | Low | Low |
| Kurnatowska | 2015 | Low | Low | Low | Low | Low | Low | Low |
| Kurnatowska | 2016 | Low | Low | Low | Low | Low | Unclear | Low |

## Supplemental Table S4

Characteristics and reported risk of cardiovascular or mortality outcomes in longitudinal studies assessing vitamin K dependent enzyme (VKDE) at baseline as continuous variable.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Year** | **VKDE measured** | **Hazard ratio measurement** | **Outcome** | **HR (95% CI)** | **P** |
| Schurgers | 2010 | dp-ucMGP | HR for 100pm increase in log-transformed dpucMGP | Mortality | 1.06 (1.02-1.10) | 0.005 |
| Dalmeijer | 2013 | dp-ucMGP | HR per change in standard deviation | Fatal and non-fatal CVD | 1.37 (1-21-1.54) | Not reported |
| Dalmeijer | 2014 | dp-ucMGP | HR per change in standard deviation | Coronary heart disease | 1.03 (0.98-1.10) | Not reported |
| Liu | 2014 | dp-ucMGP | HR per increase in dp-ucMGP (squared) | Mortality | 1.02 (1.01-1.03) | <0.001 |
| Liu | 2014 | dp-ucMGP | HR per increase in dp-ucMGP (squared) | CV events | 0.99 (0.94-1.05 | 0.87 |
| van den Heuvel | 2014 | dp-ucMGP | HR for 100pm increase in log-transformed dpucMGP | Fatal and non-fatal CVD | 1.13 (1.02-1.24) | Not reported |
| Keyzer | 2015 | dp-ucMGP | HR per increase in log transformed dp-ucMGP | Mortality | 1.65 (1.26-2.16) | <0.001 |
| Danziger | 2016 | PIVKA-II | HR per doubling of PIVKA-II | CVD (coronary heart disease, stroke, fatal CV event) | 1.46 (1.08-1.97) | 0.047 |

## Supplemental Table S5

Ongoing studies of vitamin K supplementation on vascular health (stiffness or calcification)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Trial identifier** | **Source of identifier** | **Population** | **VK dose and formulation** | **Primary endpoint** |
| NCT01742273 | Clinicaltrials.gov | Haemodialysis | K1 5mg 3x/wk | Progression of thoracic aorta and coronary calcification |
| NCT01528800 | Clinicaltrials.gov | Haemodialysis | K1 10mg 3x/wk | Progression of coronary artery calcification, cardiovascular events |
| NCT01002157 | Clinicaltrials.gov | Coronary artery calcification | K2 (MK7) dose unknown | Progression of coronary calcification |
| NCT01922804 | Clinicaltrials.gov | Postmenopausal women with osteopaenia | K2 (MK7) 375 micrograms daily | Change in bone mineral density, insulin sensitivity, arterial stiffness |
| NCT02404519 | Clinicaltrials.gov | Functional vitamin K deficiency | K2 (MK7) 180 micrograms daily | Change in arterial stiffness |
| NCT02610933 | Clinicaltrials.gov | Haemodialysis patients with atrial fibrillation | K2 (MK7) 2000 micrograms 3x/wk | Progression of thoracic aorta and coronary artery calcification, progression of arterial stiffness |
| ISRCTN21444964 | ISRCTN | Chronic kidney disease 3b/4 | K2 (MK7) 400 micrograms daily | Vascular stiffness |

## Supplemental Figure S1

Search strategy for identification of vitamin K clinical trials

(vitamin K OR menadiol OR menadione OR menaquinone OR menatetrenone OR phytonadione OR methylphytyl OR phylloquinone OR phytomenadione)

AND

(cardiovascular OR cardiac OR coronary OR vascular OR vessel OR artery OR arterial OR aorta OR stiffness OR distensibility OR calcification)

## Supplemental Figure S2

Search Strategy for identification of longitudinal studies

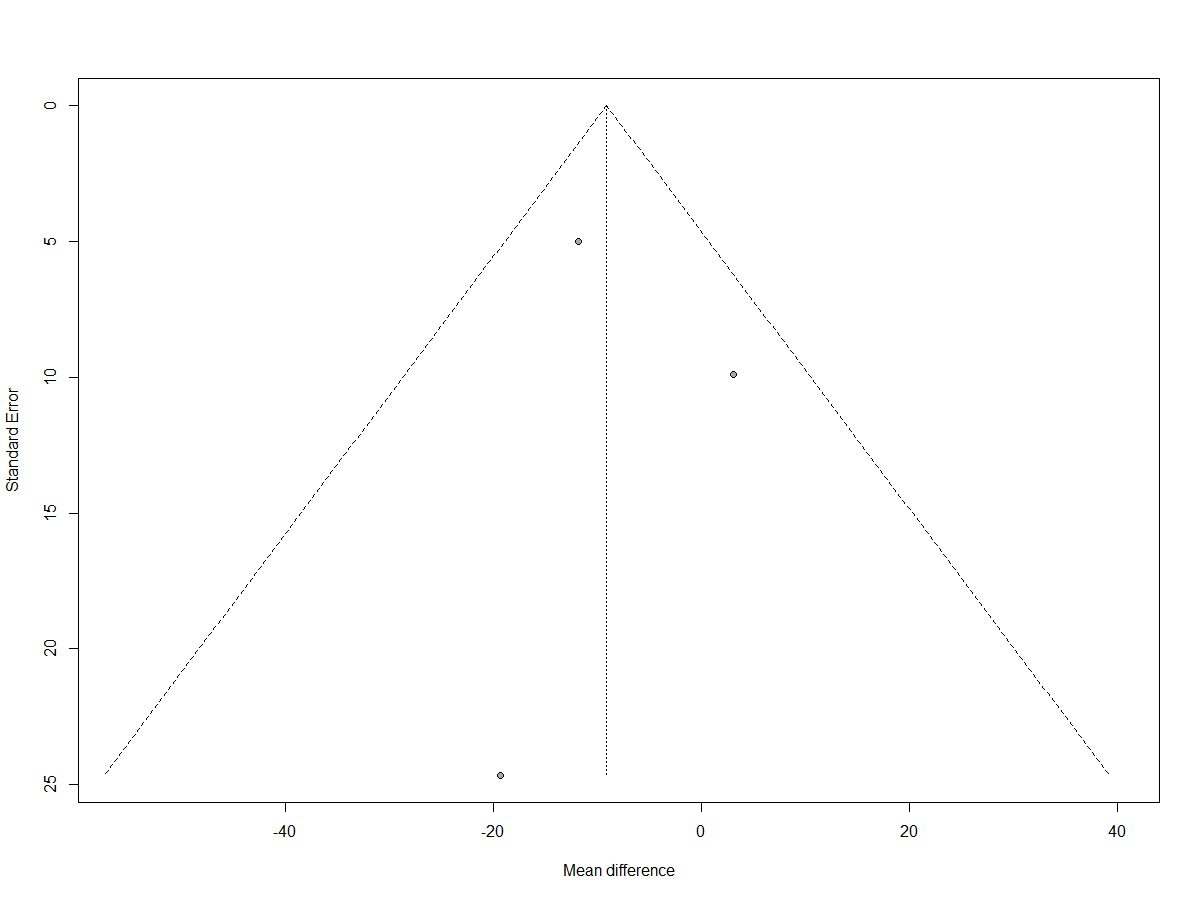
(Matrix Gla protein OR MGP OR Osteocalcin OR PIVKA OR Vitamin K deficiency)

AND

(Cardiovascular OR Coronary OR Cardiac OR CV OR Mortality OR Death)

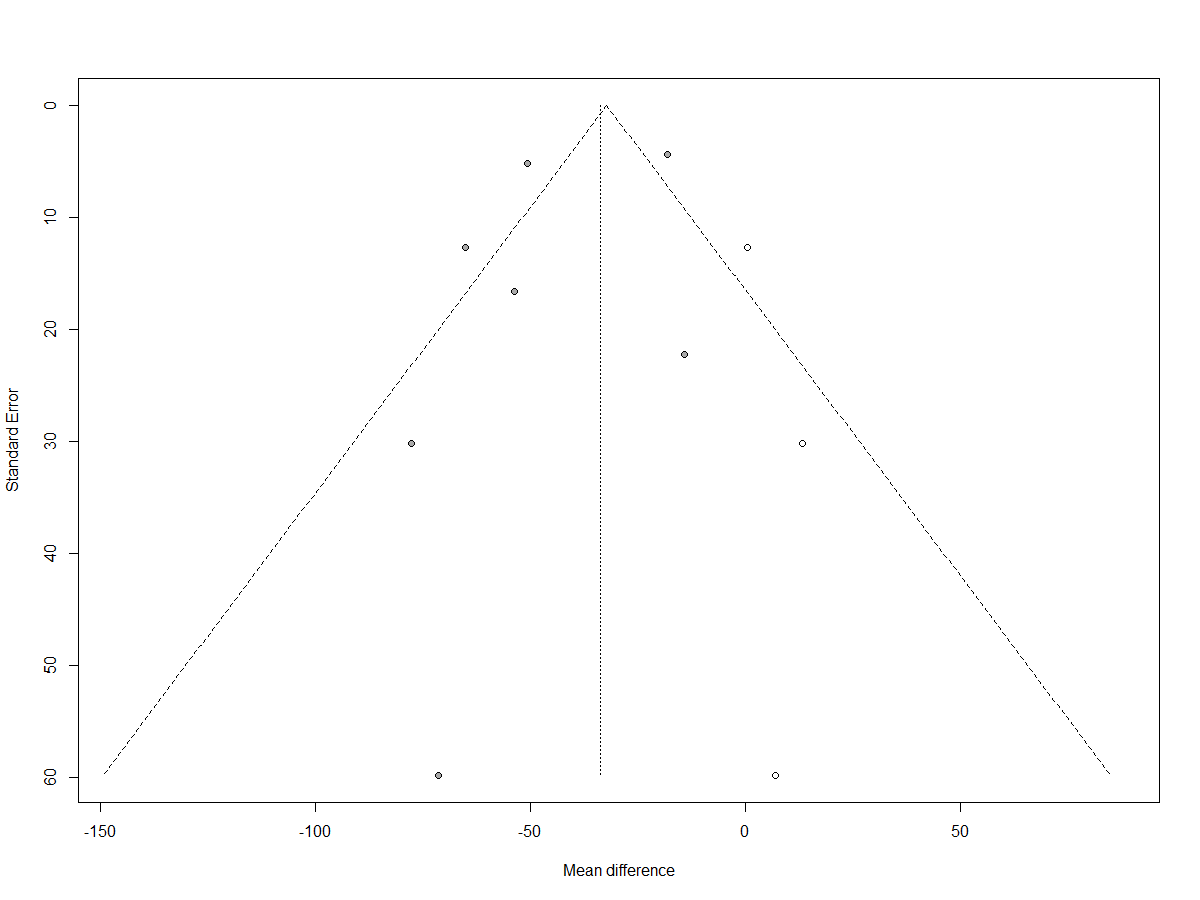
## Supplemental Figure S3

Funnel plot including Trim and Fill analysis for assessment of publication bias for vitamin K intervention studies measuring vascular calcification. Filled circles represent log hazard ratio plotted against standard error for included studies. There are no unfilled circles (which represent studies with imputed results to balance the analysis). There is no suggestion of publication bias though with few studies for comparison.



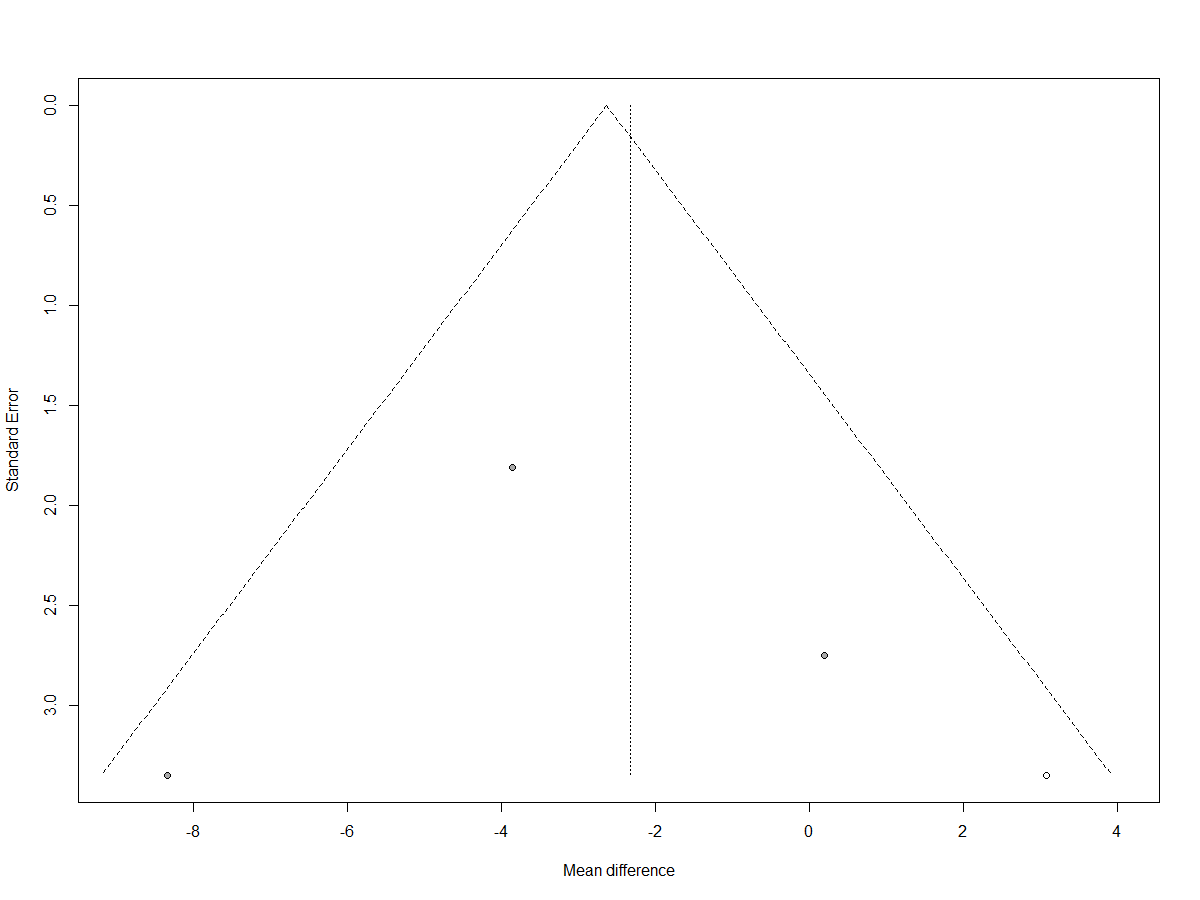
## Supplemental Figure S4

Funnel plot including Trim and Fill analysis for assessment of publication bias for vitamin K intervention studies measuring effect on dp-ucMGP. Filled circles represent log hazard ratio plotted against standard error. Unfilled circles represent studies that would be expected to balance the results. There are unfilled circles to the right suggesting publication bias in favour of positive results.



## Supplemental Figure S5

Funnel plot including Trim and Fill analysis for assessment of publication bias for vitamin K intervention studies measuring effect on vascular stiffness. Filled circles represent log hazard ratio plotted against standard error. Unfilled circles represent studies that would be expected to balance the results. There is suggestion of skew to the left (which indicates favourable improvement in vascular stiffness), and therefore suggestion of publication bias in favour of positive results.



## Supplemental Figure S6

## Supplemental Figure S7

Funnel plot including Trim and Fill analysis for assessment of publication bias for dp-ucMGP considered “high” vs “low”. Filled circles represent log hazard ratio plotted against standard error. Unfilled circles represent studies that would be expected to balance the results. There is suggestion of skew to the right i.e. publication bias in favour of positive results.

