



Chen, H. G., Sheng, L. T., Cao, A. L., Lai, Y. W., Kunutsor, S. K., Jiang, L., & Pan, A. (2019). Association of vitamin K with cardiovascular events and all-cause mortality: a systematic review and meta-analysis. *European Journal of Nutrition*, 58(6), 2191-2205. <https://doi.org/10.1007/s00394-019-01998-3>

Peer reviewed version

Link to published version (if available):
[10.1007/s00394-019-01998-3](https://doi.org/10.1007/s00394-019-01998-3)

[Link to publication record in Explore Bristol Research](#)
PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via Springer at <https://link.springer.com/article/10.1007%2Fs00394-019-01998-3>. Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available: <http://www.bristol.ac.uk/pure/user-guides/explore-bristol-research/ebr-terms/>

Association of vitamin K with cardiovascular events and all-cause mortality: a systematic review and meta-analysis

Heng-Gui Chen ¹, Li-Ting Sheng ¹, Yan-Bo Zhang ¹, An-Lan Cao ¹, Yu-Wei Lai ¹, Setor K. Kunutsor ², Limiao Jiang ¹, An Pan ^{1,*}

Author Affiliations

¹ Department of Epidemiology and Biostatistics, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, 13 Hangkong Rd, Wuhan 430030, Hubei Province, China;

² Translational Health Sciences, Bristol Medical School, University of Bristol Southmead Hospital, Bristol, United Kingdom.

*** Corresponding author:** Prof. An Pan. Department of Epidemiology and Biostatistics, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, 13 Hangkong Rd, Wuhan 430030, Hubei Province, China.

Phone: 86-27-83627309; Fax: 86-27-83627309;

E-mail address: panan@hust.edu.cn.

1 **Acknowledgments**

2 We thank Geertje W. Dalmeijer and Sabine R. Zwakenberg (Julius Center for Health
3 Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands) for
4 providing re-analyzed data on dp-ucMGP and total CVD.

5

6 **Author contributions**

7 H-GC performed the statistical analysis; contributed to the discussion, wrote the manuscript,
8 and reviewed and edited the manuscript. H-GC and L-TS conducted the research, screened
9 the references and extracted the data. Y-BZ, A-LC and Y-WL researched and proofed the
10 data. SKK transformed the data to comparison of top third with bottom third. LJ and AP
11 planned and designed the study. H-GC and AP had full access to the data in this study and
12 take complete responsibility for the integrity of the data and the accuracy of the data analysis.
13 All authors critically reviewed, discussed, and approved the final manuscript.

14

15 **Funding**

16 The work was supported by the National Key Research and Development Program of China
17 (2017YFC0907500 and 2017YFC0907504), and Hubei Province Science Fund for
18 Distinguished Young Scholars (2018CFA033).

19

20 **Conflict of interest**

21 AP reported receiving a research grant from the BY-HEALTH CO., LTD, outside the
22 submitted work. Other authors declare no conflict of interest.

23 **Abstract**

24 **Purpose:** We conducted a meta-analysis to systematically assess the prospective association
25 between vitamin K and cardiovascular disease (CVD) events and all-cause mortality.

26 **Methods:** We searched Pubmed and EMBASE through January 2019 for prospective studies
27 that reported the association of vitamin K (assessed by dietary intake or circulating
28 concentration) with CVD events (including total CVD, CVD mortality, total coronary heart
29 disease [CHD], fatal CHD, nonfatal myocardial infarction [MI] and stroke) and all-cause
30 mortality. Multivariable-adjusted hazard ratios (HRs) comparing top versus bottom tertiles of
31 vitamin K were combined using random-effects meta-analysis.

32 **Results:** Twenty-one articles were included with 222,592 participants. A significant
33 association was found between dietary phylloquinone and total CHD (pooled HR: 0.92; 95%
34 CI: 0.84, 0.99; $I^2 = 0\%$; 4 studies), as well as menaquinone and total CHD (0.70; 95% CI:
35 0.53, 0.93; $I^2 = 32.1\%$; 2 studies). No significant association was observed between dietary
36 vitamin K and all-cause mortality, CVD mortality or stroke. Elevated plasma desphospho-
37 uncarboxylated MGP (dp-ucMGP), a marker of vitamin K deficiency, was associated with an
38 increased risk of all-cause mortality (1.84; 95% CI: 1.48, 2.28; $I^2 = 16.8\%$; 5 studies) and
39 CVD mortality (1.96; 95% CI: 1.47, 2.61; $I^2 = 0\%$; 2 studies). No significant association was
40 observed between circulating total osteocalcin and all-cause mortality or total CVD.

41 **Conclusions:** Our findings showed that higher dietary vitamin K consumption was associated
42 with a moderately lower risk of CHD, and higher plasma dp-ucMGP concentration, but not
43 total circulating osteocalcin, was associated with increased risks of all-cause and CVD
44 mortality. However, causal relations cannot be established because of limited number of

45 available studies, and larger prospective studies and randomized clinical trials are needed to
46 validate the findings.

47 **Keywords:** Vitamin K; Dp-ucMGP; Osteocalcin; Cardiovascular disease; Mortality, Meta-
48 analysis

49 **Introduction**

50 Cardiovascular disease (CVD), including coronary heart disease (CHD) and stroke, is
51 still the leading cause of death and disease burden in many countries around the world [1].
52 Mounting evidence has indicated that diet plays an important role in the development of
53 CVD, and eventually death [2-5].

54 Vitamin K, a family of fat-soluble compounds, comprises both phylloquinone and
55 menaquinone. The former, also called as vitamin K1, is mainly derived from dark-green leafy
56 vegetables; while the latter, also known as vitamin K2, is primarily derived from dairy
57 products, meat, and eggs [6, 7]. Both phylloquinone and menaquinone can catalyze the γ -
58 glutamate carboxylation of all vitamin K-dependent proteins [8], such as matrix Gla protein
59 (MGP) and osteocalcin. MGP is synthesized by chondrocytes and vascular smooth muscle
60 cells and categorized into various types according to their carboxylation or phosphorylation
61 status, i.e., uncarboxylated MGP (ucMGP), carboxylated MGP (cMGP), desphosphorylated
62 MGP (dpMGP), and phosphorylated MGP (pMGP) [9]. Osteocalcin is synthesized in bone
63 during bone formation and includes both carboxylated and uncarboxylated forms [10].
64 However, no single biomarker is currently considered as a gold-standard clinical indicator of
65 vitamin K status and reference ranges of those biomarkers remain to be established. Since
66 vitamin K insufficiency leads to increase circulating concentration of desphospho-ucMGP
67 (dp-ucMGP) and total osteocalcin, which have been indicated to be markers for the
68 assessment of circulating vitamin K status [10, 11], with higher dp-ucMGP and osteocalcin
69 concentrations reflecting lower vitamin K status [9-11]. The current evidence on vitamin K
70 and risk of CVD events and death is equivocal because of limited observational studies and

71 clinical trials [12-14]. A recent meta-analysis summarized data from cohort studies up to
72 December 2017 [15], and reported that higher plasma concentrations of dp-ucMGP, but not
73 dietary intakes of vitamin K, were associated with an increased risk of total and CVD
74 mortality. However, the associations between dietary intake and incident CVD and other
75 circulating vitamin K biomarkers such as osteocalcin were not reported.

76 Therefore, we performed a systematic review and quantitative evaluation of most
77 updated evidence to add substantive new data and insights into the association of vitamin K
78 exposure, involving studies of dietary vitamin K intake and circulating concentration of
79 vitamin K (assessed by dp-ucMGP and osteocalcin), with risks of CVD events and all-cause
80 mortality.

81

82 **Methods**

83 **Search strategy**

84 We conducted the meta-analysis following the PRISMA guidelines for performing and
85 reporting meta-analyses of observational studies [16]. We searched the literature in PubMed
86 (<http://www.ncbi.nlm.nih.gov/pubmed>) and EMBASE (<http://www.embase.com>) from
87 inception until February 2018 in the first round, and we updated the articles from February
88 2018 to January 2019 and added “osteocalcin” as an exposure (from inception until January
89 2019) in the second round. Besides, we also reviewed the reference lists of all retrieved
90 relevant articles and reviews [12-15]. Our study focused on the exposure (dietary vitamin K
91 or vitamin K biomarkers) with multiple outcomes (CVD, type 2 diabetes and mortality). Full
92 search strategies are reported in the **Supplemental material**. This article focused on the

93 association of dietary vitamin K, circulating dp-ucMGP and total osteocalcin with CVD
94 events and all-cause mortality, while the other blood biomarkers (e.g., cMGP, ucMGP,
95 carboxylated and undercarboxylated osteocalcin) and other outcomes (type 2 diabetes and
96 cause-specific mortality other than CVD mortality) were not analyzed due to very limited
97 numbers of articles.

98

99 **Study selection**

100 Eligibility of literature was independently assessed by two researchers (H-GC and L-
101 TS), and any inconsistencies were settled by consensus or consultation with a third author
102 (AP). Publications were included in the current study if they: 1) were peer-reviewed and
103 reported original results (e.g., not editorial, letter, commentary, meeting abstract, or review
104 article); 2) were cohort studies (i.e., the exposure status was measured before the onset of the
105 outcome, including prospective or retrospective designs); 3) were published in English; 4)
106 included non-institutionalized adults older than 18 years old without CVD at baseline; and 5)
107 reported an association between dietary vitamin K, circulating dp-ucMGP or total
108 osteocalcin, and at least one specific CVD events (i.e., total CVD, CVD mortality, total CHD,
109 fatal CHD, nonfatal myocardial infarction [MI] and stroke) or all-cause mortality using
110 multivariable-adjusted risk estimates. Potentially eligible publications were included through
111 an initial screening of relevant titles or abstracts, accompanied by a full-text review.

112

113 **Data extraction and quality assessment**

114 The following information from each study was independently extracted by two

115 researchers (H-GC and L-TS) using a standardized spreadsheet: citation, first author,
116 publication year, study name, study location, participants characteristics (number, mean age
117 or age range, sex composition), follow-up time, main exposure (phylloquinone,
118 menaquinone, dp-ucMGP, osteocalcin, assessment method), main endpoints (CVD events,
119 all-cause mortality, diagnostic methods and number of cases), analysis strategy (statistical
120 methods, confounding factors considered in the models), and multivariable-adjusted hazard
121 ratio (HR) estimates with corresponding 95% confidence interval (CI). We contacted study
122 authors when the data were unclear or unavailable from the identified papers. The Newcastle-
123 Ottawa Scale [17], which included items related to the comparability of study design and
124 analysis, selection bias, exposure and outcome measurements, exclusion of outcome at
125 baseline, years of follow-up, response rate, confounding adjustment, and generalizability to
126 other populations, was utilized to evaluate the study quality.

127

128 **Statistical analysis**

129 HR estimates adjusted for the maximum number of covariates were pooled across
130 studies separately for each outcome using a random-effects meta-analysis. Both categorical
131 and continuous variables of vitamin K exposure status were used in the literature, and to
132 achieve a consistent comparison of the results, we transformed the HR from each study to a
133 risk estimate that compared the top with bottom tertiles of the exposure using methods
134 described previously [18, 19]. In brief, these transformed estimates were calculated by
135 multiplying the log risk ratio and the upper and lower confidence limits with a conversion
136 factor (2.18 for a 1 SD increase, 2.18/2.54 for quartiles, and 2.18/2.80 for quintiles). The risk

137 estimates were transformed assuming that a transformation of the exposure was normally
138 distributed and a log-linear association with the outcome [18, 19].

139 Forest plots were drawn to intuitively visualize the HRs and corresponding 95% CIs
140 across studies for each outcome using a random-effects model [20]. Heterogeneity of HRs
141 was evaluated by calculating the Cochran Q statistic ($P < 0.10$ was deemed to be statistically
142 significant) and the I^2 statistic (values of 0-25%, 26-50%, 51%-75%, and 76-100% were
143 considered as having low, modest, moderate, and high likelihood of heterogeneity,
144 respectively) [21]. A sensitivity analysis was conducted using untransformed data from the
145 comparisons of the extreme categories reported in the original papers, and thus studies with
146 continuous variables of vitamin K intake/status were not included in this analysis. We did not
147 perform the sensitivity analysis of omitting one study a time because of limited number of
148 studies. All analytical procedures were conducted with Stata version 13.1 (StataCorp, College
149 Station, Texas); a 2-sided α of 0.05 was chosen for the cutoff of significance.

150

151 **Results**

152 **Literature search**

153 The literature search retrieved 19,027 publications, of which 282 were assessed in full-
154 text following a selection of titles and abstracts. Besides, an extra 2 articles were found from
155 the bibliographies of relevant reviews. After detailed examinations, 263 articles were
156 excluded and 21 original articles met our inclusion criteria and involved a total of 222,592
157 participants [22-42] (**Fig. 1**). Among the 263 articles that were excluded based on a full-text
158 review, 4 articles met the other inclusion criteria but were excluded because of data format

159 issues [43-46]. The characteristics of these 4 studies are depicted in **Table S1** and the results
160 of these studies were described in the respective text below. Among the 21 articles that were
161 included in the meta-analysis, 7 studies specifically reported dietary vitamin K as the
162 exposure [22-28], 8 studies specifically reported plasma dp-ucMGP as the exposure [29-36],
163 and 6 studies specifically reported circulating total osteocalcin as the exposure [37-42].

164

165 **Included study characteristics**

166 All 21 eligible articles were derived from prospective cohort studies. Seven studies
167 investigated associations of dietary vitamin K and CVD events, 5 studies investigated
168 associations of plasma dp-ucMGP with CVD events, 4 studies investigated associations of
169 circulating total osteocalcin with total CVD, and 3 dietary vitamin K studies, 5 plasma dp-
170 ucMGP studies and 2 circulating total osteocalcin studies explored the associations with all-
171 cause mortality, respectively. In all studies, dietary vitamin K consumption was evaluated
172 through validated food frequency questionnaires (FFQs), dp-ucMGP concentration was
173 determined in plasma by ELISA method, and total osteocalcin was quantified using different
174 assays such as electrochemiluminescent immunoassay, radioimmunoassay and enzyme
175 immune assay and automated Elecsys assay, etc. Study samples ranged from 95 to 72,874,
176 and the mean or median follow-up duration ranged from 1.9 to 16.8 years. Fifteen studies
177 were conducted in European countries (The Netherlands, Spain, France and Czech Republic),
178 3 studies were conducted in Asian countries (Japan and South Korea), and the other 2 and 1
179 studies were done in the United States (U.S.) and Australia, respectively. Crude HR was
180 transformed in study by Yeap et al [37], 2 study adjusted for socio-demographic

181 characteristics, and 10 studies corrected for socio-demographic characteristics (e.g., age, sex)
182 and established CVD risk factors (e.g., lifestyle factors and complications) and the other 8
183 studies additionally corrected for dietary intakes or biomarker concentration of other vitamins
184 (e.g., vitamin D) (**Table 1**). Overall, the Newcastle-Ottawa Scale awarded scores ranged from
185 6 to 9, indicating moderate to high methodological quality of all studies (**Table S2**).

186

187 **Dietary vitamin K with CVD events and all-cause mortality**

188 A total of 7 articles reported on the associations of dietary vitamin K (phylloquinone and
189 menaquinone) with CVD events (i.e., CVD mortality, total CHD, fatal CHD, nonfatal MI and
190 stroke) and all-cause mortality. For dietary phylloquinone, the association was only
191 statistically significant with total CHD (pooled HR comparing top with bottom tertiles: 0.92;
192 95% CI: 0.84, 0.99; $P = 0.035$; $I^2 = 0\%$; 4,249 cases from 4 studies). Modest associations
193 were found between phylloquinone and fatal CHD (pooled HR comparing top with bottom
194 tertiles: 0.89; 95% CI: 0.77, 1.02; $P = 0.082$; $I^2 = 0\%$; 1,503 cases from 4 studies) and
195 nonfatal MI (pooled HR comparing top with bottom tertiles: 0.91; 95% CI: 0.82, 1.02; $P =$
196 0.100 ; $I^2 = 0\%$; 2,604 cases from 3 studies). No statistically significant associations were
197 found with other CVD subtypes (i.e., stroke and CVD mortality) (**Fig. 2**). For dietary
198 menaquinone, similar results were obtained for total CHD (pooled HR comparing top with
199 bottom tertiles: 0.70; 95% CI: 0.53, 0.93; $P = 0.014$; $I^2 = 32.1\%$; 713 cases from 2 studies).
200 There were no statistically significant associations of dietary menaquinone with fatal CHD
201 and CVD mortality (**Fig. 3**). In the sensitivity analysis using untransformed data based on
202 extreme categories of exposure, the findings were generally remained (**Fig. S1 and S2**).

203 Three studies reported the association of both dietary phylloquinone and menaquinone as the
204 exposure with all-cause mortality [22, 27, 28], and no significant associations were found
205 (**Fig. 4**), nor in the sensitivity analysis using untransformed data (**Fig. S3**).

206 The study by Cheung et al. [43] was excluded because of data format issue. In this study,
207 3,401 participants with chronic kidney disease (CKD) from the Third National Health and
208 Nutrition Examination Survey (NHANES III) were classified into two groups based on their
209 total vitamin K intake levels higher or lower than the recommended adequate intake level (90
210 $\mu\text{g}/\text{d}$ for women and 120 $\mu\text{g}/\text{d}$ for men, respectively), and it was reported that higher dietary
211 vitamin K intake at baseline was associated with a 15% reduced risk of all-cause mortality
212 (HR: 0.85; 95 CI%: 0.72, 1.00; 1,815 cases) and a 22% reduced risk of CVD mortality (HR:
213 0.78; 95 CI%: 0.64, 0.95; 876 cases) during a median follow-up of 13.3 years (**Table S1**).
214 Thus, our conclusion would not be substantially changed if this study was included.

215

216 **The association of circulating dp-ucMGP and total osteocalcin with all-cause mortality**

217 A significant positive association was observed between plasma concentrations of dp-
218 ucMGP and all-cause mortality (pooled HR comparing top with bottom tertiles: 1.84; 95%
219 CI: 1.48, 2.28; $P < 0.001$; 483 cases from 5 studies) with low heterogeneity ($I^2 = 16.8\%$) (**Fig.**
220 **5**). The results were not materially changed if the untransformed data were used in the
221 sensitivity analysis (**Fig. S4**). However, it should be noted that all five studies were conducted
222 in patients with certain diseases (e.g., symptomatic aortic stenosis [29], chronic kidney
223 disease [30], type 2 diabetes [31], stable kidney transplantation [34] or heart failure patients
224 with vascular disease [35]). Most of the patients were taking vitamin K antagonists, which

225 may explain why their median dp-ucMGP concentrations ranged from 156 to 1,038 pmol/L
226 (average median = 784.8 pmol/L), much higher than the general population (for example, 114
227 pmol/L in the EPIC-NL study among general participants [33]). No statistically significant
228 association was found between circulating total osteocalcin and all-cause mortality (pooled
229 HR comparing top with bottom tertiles: 1.07; 95% CI: 0.59, 1.96; $P = 0.82$; 628 cases from 2
230 studies) (**Fig. 6**).

231 Two studies have examined the association between plasma dp-ucMGP concentrations
232 and all-cause mortality in the general population, but they were not included in our meta-
233 analysis because of data format issue (**Table S1**). Liu et al. [44] followed 2,318 participants
234 in Belgium for a median of 14.1 years and reported a J-shaped association with a nadir at 135
235 pmol/L, and dp-ucMGP was positively and linearly associated with all-cause mortality above
236 the level of 135 pmol/L. Riphagen et al. [45] followed 4,275 participants in The Netherlands
237 for a median of 8.5 years and also reported a J-shaped association with a threshold at 414
238 pmol/L, and positive and linear association was found when dp-ucMGP levels were above
239 414 pmol/L, while the association was flat below this level. Given that these two studies both
240 reported a J-shape association but with different nadir, more studies are still needed to
241 confirm and quantify the association in the general population.

242

243 **The association of circulating dp-ucMGP and total osteocalcin with CVD events**

244 Three studies [31, 32, 36] investigated the association between plasma dp-ucMGP
245 concentration and risk of total CVD, the overall pooled HR (95% CI) comparing top with
246 bottom tertiles was 1.57 (1.19, 2.06; $P < 0.001$; $I^2 = 1.1\%$; 220 cases from 3 studies) (**Fig. 5**).

247 The study by Shea et al. [46] was not included because we cannot transform the HR to a risk
248 estimate that compared the top with bottom tertiles based on existing data (**Table S1**). In this
249 study, 635 community-dwelling adults aged 70–79 y from the U.S. were classified into two
250 groups based on their dp-ucMGP concentrations higher or lower than the predefined cut-off
251 values (574 pmol/L), and it was reported that higher plasma dp-ucMGP concentration was
252 not significantly associated with a higher risk of total CVD (HR: 1.02; 95 CI%: 0.72, 1.45;
253 169 cases). We included this study in the sensitivity analysis using untransformed data based
254 on extreme categories of exposure, and the pooled HR became insignificant (1.13; 95% CI:
255 0.80, 1.62; $I^2 = 29.5\%$; 4 studies) (**Fig. S4**). Moreover, no statistically significant associations
256 were found between circulating total osteocalcin and total CVD (pooled HR comparing top
257 with bottom tertiles: 1.02; 95% CI: 0.76, 1.36; $P = 0.917$; 946 cases from 4 studies) (**Fig. 6**),
258 nor in the sensitivity analysis using untransformed data (**Fig. S5**).

259 Two studies [31, 35] reported the association between plasma dp-ucMGP concentration
260 and risk of CVD mortality, the overall pooled HR (95% CI) comparing top with bottom
261 tertiles was 1.96 (1.47, 2.61; $P < 0.001$; $I^2 = 0\%$; 143 cases from 2 studies) (**Fig. 5**). A similar
262 result was obtained in the sensitivity analysis (**Fig. S4**). The above-mentioned study by Liu et
263 al. [44] was not included because they reported that higher levels of dp-ucMGP were log-
264 linearly associated with increased CVD mortality (HR for per doubling of the nadir: 1.14;
265 95% CI: 1.01, 1.28; 70 cases), but insignificantly associated with risk of total CVD (HR for
266 per doubling of the nadir: 0.99; 95% CI: 0.94, 1.05; 180 cases). The above-mentioned study
267 by Riphagen et al. [45] was also not included because they reported a J-shaped association
268 with CVD mortality, and positive and linear association was found when dp-ucMGP levels

269 were above 557 pmol/L.

270 Regarding to other types of CVD events, a study from The Netherlands [33] reported
271 insignificant associations of plasma dp-ucMGP concentration with risk of total CHD (HR
272 comparing extreme quartiles: 0.94; 95% CI: 0.79, 1.13; 1,252 cases) and stroke (HR
273 comparing extreme quartiles: 1.09; 95% CI: 0.78, 1.51; 405 cases) in the general population.
274 The above-mentioned study by Liu et al. [44] also reported that higher levels of dp-ucMGP
275 were log-linearly associated with decreased risk of coronary events (HR for per doubling of
276 the nadir: 0.93; 95% CI: 0.88, 0.99; 85 cases), but insignificantly associated with stroke risk
277 (HR for per doubling of the nadir: 0.98; 95% CI: 0.81, 1.19; 29 cases). A study from South
278 Korea [40] reported insignificant associations of circulating total osteocalcin with risk of
279 incident CHD (HR comparing extreme tertiles: 1.05; 95% CI: 0.44, 2.50; 29 cases) and stroke
280 (HR comparing extreme tertiles: 0.69; 95% CI: 0.34, 1.39; 47 cases) in middle-aged men.

281

282 **Discussion**

283 We systematically investigated the associations of vitamin K with CVD events and all-
284 cause mortality using data from both dietary and biomarker studies. Our results suggested
285 that higher dietary phylloquinone and menaquinone intakes were consistently associated with
286 a lower risk of total CHD, and higher dp-ucMGP concentration was associated with a higher
287 risk of all-cause and CVD mortality. Generally, these data support potential benefits of
288 vitamin K on the prevention of CVD events and all-cause mortality. However, given that no
289 significant association was found for osteocalcin with the outcomes, and the number of
290 included studies was small, consensus cannot be made and more studies are still needed.

291 In our current meta-analysis, we found that higher dietary intakes of phylloquinone and
292 menaquinone intake were associated with a lower risk of total CHD and a trend of lower risk
293 but not statistically significant association with fatal CHD. The association appeared to be
294 stronger for menaquinone. It is possible that phylloquinone and menaquinone are mainly
295 transported by chylomicrons, from where phylloquinone is more effectively cleared by the
296 liver. Long residence periods of higher menaquinone indicate that it is favorable for
297 extrahepatic tissue such as arterial vessel uptake for much longer durations than
298 phylloquinone [6]. However, the lower risk of CHD related to dietary phylloquinone could be
299 a reflection of a healthy diet because the main dietary sources are green vegetables and
300 vegetable oils [6, 7]. By contrast, the associations between menaquinone and CHD risks were
301 unlikely due to confounding by a healthier diet since menaquinone is primarily derived from
302 dairy products, meat, and eggs, and the associations between those food groups and CHD
303 risks were not entirely consistent: no significant association was found for dairy [47] and egg
304 [48], while increased risk was found for meat [49], particularly processed red meat.
305 Therefore, the inverse association between menaquinone and CHD risks cannot be explained
306 by the food sources. Given the limited number of identified articles, firm conclusions cannot
307 be made, and further investigations are warranted to verify the associations of dietary vitamin
308 K consumption and CHD risks.

309 Higher plasma dp-ucMGP concentration has been consistently reported to be associated
310 with increased risks of all-cause mortality in several original studies [29-31, 34, 35].
311 Empirically, target biomarker measured in plasma may provide more objective nutritional
312 assessment than dietary records [50]. In the dietary studies, the intakes of vitamin K were all

313 self-reported using FFQs. The accuracy of FFQs data depends on memory and precise
314 estimation of the frequency and portion size of the foods over a specified period (typically the
315 past year), as well as the quality of the food composition table used to estimate the dietary
316 vitamin K consumption [51]. It is possible that both random and systematic measurement
317 errors were inevitable because of imperfect recalls, omissions of vitamin K containing food
318 items in the FFQs [e.g., extended food composition data for vitamin K to support the notable
319 contributions made by convenience foods and composite dishes] and inaccurate information
320 in the dietary databases [52, 53]. Therefore, we cannot draw a firm conclusion regarding the
321 role of dietary intakes of vitamin K on CVD events and all-cause mortality. On the other
322 hand, plasma dp-ucMGP concentration is an objective biomarker that may reflect vitamin K
323 status and can avoid the aforesaid measurement errors. However, the plasma dp-ucMGP
324 concentration may only reflect short-term vitamin K exposure status owing to the short half-
325 life of vitamin K [20, 54], and age, gender/ethnicity, lifestyle, metabolic health status may
326 influence of dp-ucMGP concentration. Although circulating total osteocalcin is thought to be
327 a sensitive marker to reflect vitamin K status, we did not find any significant associations
328 between total osteocalcin and all-cause mortality or total CVD. It is possible that dp-ucMGP
329 is the main vitamin K status indicator of vascular calcification, while total osteocalcin is
330 related to bone formation [55]. Therefore, consistent with the scientific opinion provided by
331 European Food Safety Authority (EFSA) panel [56], we also considered that available data on
332 dietary intake of phylloquinone or menaquinones and health outcomes cannot be utilized to
333 derive dietary reference values (DRVs) for vitamin K, and no biomarkers of vitamin K intake
334 or status is currently applicable to derive DRVs for vitamin K.

335 Very few randomized clinical trials have been performed to evaluate the effects of
336 vitamin K supplementation on cardiovascular health. A 3-year double-blind, randomized
337 controlled trial conducted among 388 community-dwelling men and women (60-80 years) in
338 the U.S. showed that daily supplementation of a multivitamin with 500 µg phylloquinone
339 reduced the progression of existing coronary artery calcification (CAC) compared with a
340 daily multivitamin without phylloquinone [57]. In a study with 80 healthy post-menopausal
341 women in The Netherlands, Knapen et al. [58] revealed that long-term (36 months)
342 supplementation with 180 µg/d menaquinone improved arterial stiffness compared with those
343 receiving placebo. Results from the two clinical trials support the view that vitamin K is
344 beneficial in reducing CVD events. Mechanistically, phylloquinone and menaquinone act as
345 cofactors to catalyze the carboxylation of glutamic acid residues (Glu) into γ -
346 carboxylglutamate (Gla) [8], which binds with free calcium ions to inhibit vascular
347 calcification [59]. Therefore, higher levels of vitamin K may reduce vascular calcification
348 [60-62], and consequently lowers the risks of CVDs and death. However, the current
349 evidence is still limited to set optimal intake levels of vitamin K, and this needs to be
350 confirmed in future studies.

351 Several limitations of this meta-analysis should be noted. First, although we conducted a
352 comprehensive literature search, a relatively small number of articles were included, which
353 limited our capacity to conduct more subgroup analyses (e.g., stratification by age, sex,
354 participant characteristics, CVD subtypes, disease state and medication use) and to identify
355 the source of heterogeneity. More high-quality prospective studies are certainly needed.

356 Second, we included plasma dp-ucMGP and total osteocalcin as biomarkers to reflect vitamin

357 K status, but all included studies did not correct for total MGP concentrations and calculate
358 the proportion of undercarboxylated osteocalcin in their analyses. Therefore, the observed
359 association of dp-ucMGP and total osteocalcin with CVD events and all-cause mortality
360 might be influenced since dp-ucMGP and total osteocalcin concentrations may not
361 necessarily reflect vitamin K intake. Third, we only included publications in English and
362 excluded articles which did not meet our data format requirements, thus the possibility of bias
363 cannot be ruled out. Fourth, the confounding factors adjusted for in the original articles varied
364 across studies, and residual confounding cannot be completely excluded. The baseline levels
365 for vitamin K intakes or circulating biomarker concentrations also varied across studies and
366 we could not directly report the levels across tertiles in the pooled analyses. Notwithstanding,
367 we examined the prospective associations of both dietary and biomarkers of vitamin K status
368 with CVD outcomes and all-cause mortality by summarizing the most updated evidence.
369 Compared to the prior meta-analysis [15], we additionally included studies of dietary vitamin
370 K intakes with CVD risk, and also circulating osteocalcin concentrations with CVD outcomes
371 and all-cause mortality. In addition, the prior meta-analysis [15] reported the pooled HR
372 comparing the extreme categories, while we were able to transform risk estimates from most
373 original studies to a consistent comparison of top versus bottom tertiles, which may provide
374 more comparable estimates.

375 In summary, our meta-analysis provides further insight that higher vitamin K levels at
376 baseline, as evaluated by both dietary intake and plasma dp-ucMGP concentration, may be
377 associated with a lower risk of total CHD and all-cause mortality, respectively. However, we
378 did not find significant associations between total osteocalcin and total CVD and all-cause

379 mortality. Therefore, our results need to be interpreted with caution due to the limited
380 number, inconsistent results and potential confounding issues of included studies. Since our
381 study cannot infer causality, high-quality prospective cohort studies in different populations
382 and randomized clinical trials are still required to draw a firm conclusion regarding the role
383 of vitamin K in cardiovascular health and death.

384

References

1. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators (2017) Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 390 (10100):1211-1259.
[https://doi.org/10.1016/S0140-6736\(17\)32154-2](https://doi.org/10.1016/S0140-6736(17)32154-2)
2. Pan A, Lin X, Hemler E, Hu FB (2018) Diet and cardiovascular disease: advances and challenges in population-based studies. *Cell Metab* 27 (3):489-496.
<https://doi.org/10.1016/j.cmet.2018.02.017>
3. Du H, Li L, Bennett D, Guo Y, Key TJ, Bian Z, Sherliker P, Gao H, Chen Y, Yang L, Chen J, Wang S, Du R, Su H, Collins R, Peto R, Chen Z, China Kadoorie Biobank S (2016) Fresh fruit consumption and major cardiovascular disease in China. *N Engl J Med* 374 (14):1332-1343. <https://doi.org/10.1056/NEJMoa1501451>
4. Wang X, Ouyang Y, Liu J, Zhu M, Zhao G, Bao W, Hu FB (2014) Fruit and vegetable consumption and mortality from all causes, cardiovascular disease, and cancer: systematic review and dose-response meta-analysis of prospective cohort studies. *BMJ* 349:g4490. <https://doi.org/10.1136/bmj.g4490>
5. Scarborough P, Morgan R, Webster P, Rayner M (2011) Differences in coronary heart disease, stroke and cancer mortality rates between England, Wales, Scotland and Northern Ireland: the role of diet and nutrition. *BMJ Open* 1 (1):e000263.
<https://doi.org/10.1136/bmjopen-2011-000263>

6. Schurgers LJ, Vermeer C (2000) Determination of phylloquinone and menaquinones in food. Effect of food matrix on circulating vitamin K concentrations. *Haemostasis* 30 (6):298-307. <https://doi.org/54147>
7. Shearer MJ (1995) Vitamin K. *Lancet* 345 (8944):229-234
8. Furie B, Bouchard BA, Furie BC (1999) Vitamin K-dependent biosynthesis of gamma-carboxyglutamic acid. *Blood* 93 (6):1798-1808
9. Dalmeijer GW, van der Schouw YT, Vermeer C, Magdeleyns EJ, Schurgers LJ, Beulens JWJ (2013) Circulating matrix Gla protein is associated with coronary artery calcification and vitamin K status in healthy women. *J Nutr Biochem* 24 (4):624-628. <https://doi.org/10.1016/j.jnutbio.2012.02.012>
10. Shea MK, Booth SL (2016) Concepts and controversies in evaluating vitamin K status in population-based studies. *Nutrients* 8. <https://doi.org/10.3390/nu8010008>.
11. Cranenburg EC, Koos R, Schurgers LJ, Magdeleyns EJ, Schoonbrood TH, Landewe RB, Brandenburg VM, Bekers O, Vermeer C (2010) Characterisation and potential diagnostic value of circulating matrix Gla protein (MGP) species. *Thromb Haemost* 104 (4):811-822. <https://doi.org/10.1160/TH09-11-0786>
12. Rees K, Guraewal S, Wong YL, Majanbu DL, Mavrodaris A, Stranges S, Kandala NB, Clarke A, Franco OH (2010) Is vitamin K consumption associated with cardio-metabolic disorders? A systematic review. *Maturitas* 67 (2):121-128. <https://doi.org/10.1016/j.maturitas.2010.05.006>
13. Hartley L, Clar C, Ghannam O, Flowers N, Stranges S, Rees K (2015) Vitamin K for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev*

(9):Cd011148. <https://doi.org/10.1002/14651858.CD011148.pub2>

14. Harshman SG, Shea MK (2016) The role of vitamin K in chronic aging diseases: inflammation, cardiovascular disease, and osteoarthritis. *Curr Nutr Rep* 5 (2):90-98. <https://doi.org/10.1007/s13668-016-0162-x>

15. Zhang S, Guo L, Bu C (2018) Vitamin K status and cardiovascular events or mortality: a meta-analysis. *Eur J Prev Cardiol*:2047487318808066. <https://doi.org/10.1177/2047487318808066>

16. Moher D, Liberati A, Tetzlaff J, Altman D (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 6 (7):e1000097

17. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, P. T (2012) The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (cited 1 June 2018).

18. Danesh J, Collins R, Appleby P, Peto R (1998) Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. *JAMA* 279 (18):1477-1482. <https://doi.org/10.1001/jama.279.18.1477>

19. Chêne G, Thompson SG (1996) Methods for summarizing the risk associations of quantitative variables in epidemiologic studies in a consistent form. *Am J Epidemiol* 144 (6):610-621. <https://doi.org/10.1093/oxfordjournals.aje.a008971>

20. Combettes E, Mazoit JX, Benhamou D, Beloeil H (2015) Modelling of vitamin K

half-life in patients treated with vitamin K antagonists before hip fracture surgery.

Anaesth Crit Care Pa 34 (5):295-299. <https://doi.org/10.1016/j.accpm.2015.06.003>

21. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. *BMJ* 327 (7414):557-560. <https://doi.org/10.1136/bmj.327.7414.557>

22. Geleijnse JM, Vermeer C, Grobbee DE, Schurgers LJ, Knapen MH, van der Meer IM, Hofman A, Witteman JC (2004) Dietary intake of menaquinone is associated with a reduced risk of coronary heart disease: the Rotterdam Study. *J Nutr* 134 (11):3100-3105 <https://doi.org/10.1093/jn/134.11.3100>

23. Erkkila AT, Booth SL, Hu FB, Jacques PF, Manson JE, Rexrode KM, Stampfer MJ, Lichtenstein AH (2005) Phylloquinone intake as a marker for coronary heart disease risk but not stroke in women. *Eur J Clin Nutr* 59 (2):196-204. <https://doi.org/10.1038/sj.ejcn.1602058>

24. Erkkila AT, Booth SL, Hu FB, Jacques PF, Lichtenstein AH (2007) Phylloquinone intake and risk of cardiovascular diseases in men. *Nutr Metab Cardiovasc Dis* 17 (1):58-62. <https://doi.org/10.1016/j.numecd.2006.03.008>

25. Gast GC, de Roos NM, Sluijs I, Bots ML, Beulens JW, Geleijnse JM, Witteman JC, Grobbee DE, Peeters PH, van der Schouw YT (2009) A high menaquinone intake reduces the incidence of coronary heart disease. *Nutr Metab Cardiovasc Dis* 19 (7):504-510. <https://doi.org/10.1016/j.numecd.2008.10.004>

26. Vissers LE, Dalmeijer GW, Boer JM, Monique Verschuren WM, van der Schouw YT, Beulens JW (2013) Intake of dietary phylloquinone and menaquinones and risk of stroke. *J Am Heart Assoc* 2 (6):e000455. <https://doi.org/10.1161/jaha.113.000455>

27. Juanola-Falgarona M, Salas-Salvado J, Martinez-Gonzalez MA, Corella D, Estruch R, Ros E, Fito M, Aros F, Gomez-Gracia E, Fiol M, Lapetra J, Basora J, Lamuela-Raventos RM, Serra-Majem L, Pinto X, Munoz MA, Ruiz-Gutierrez V, Fernandez-Ballart J, Bullo M (2014) Dietary intake of vitamin K is inversely associated with mortality risk. *J Nutr* 144 (5):743-750.
<https://doi.org/10.3945/jn.113.187740>
28. Zwakenberg SR, den Braver NR, Engelen AI, Feskens EJ, Vermeer C, Boer JM, Verschuren WM, van der Schouw YT, Beulens JW (2016) Vitamin K intake and all-cause and cause specific mortality. *Clin Nutr* 36(5):1294-1300.
<https://doi.org/10.1016/j.clnu.2016.08.017>
29. Ueland T, Gullestad L, Dahl CP, Aukrust P, Aakhus S, Solberg OG, Vermeer C, Schurgers LJ (2010) Undercarboxylated matrix Gla protein is associated with indices of heart failure and mortality in symptomatic aortic stenosis. *J Intern Med* 268 (5):483-492. <https://doi.org/10.1111/j.1365-2796.2010.02264.x>
30. Schurgers LJ, Barreto DV, Barreto FC, Liabeuf S, Renard C, Magdeleyns EJ, Vermeer C, Choukroun G, Massy ZA (2010) The circulating inactive form of matrix Gla protein is a surrogate marker for vascular calcification in chronic kidney disease: a preliminary report. *Clin J Am Soc Nephrol* 5:568-575. <https://doi.org/10.2215/CJN.07081009>.
31. Dalmeijer GW, van der Schouw YT, Magdeleyns EJ, Vermeer C, Verschuren WM, Boer JM, Beulens JW (2013) Matrix Gla protein species and risk of cardiovascular events in type 2 diabetic patients. *Diabetes Care* 36 (11):3766-3771.

<https://doi.org/10.2337/dc13-0065>

32. van den Heuvel EG, van Schoor NM, Lips P, Magdeleyns EJ, Deeg DJ, Vermeer C, den Heijer M (2014) Circulating uncarboxylated matrix Gla protein, a marker of vitamin K status, as a risk factor of cardiovascular disease. *Maturitas* 77 (2):137-141.

<https://doi.org/10.1016/j.maturitas.2013.10.008>

33. Dalmeijer GW, van der Schouw YT, Magdeleyns EJ, Vermeer C, Verschuren WM, Boer JM, Beulens JW (2014) Circulating desphospho-uncarboxylated matrix gamma-carboxyglutamate protein and the risk of coronary heart disease and stroke. *J Thromb Haemost* 12 (7):1028-1034.

<https://doi.org/10.1111/jth.12609>

34. Keyzer CA, Vermeer C, Joosten MM, Knapen MH, Drummen NE, Navis G, Bakker SJ, de Borst MH (2015) Vitamin K status and mortality after kidney transplantation: a cohort study. *Am J Kidney Dis* 65 (3):474-483.

<https://doi.org/10.1053/j.ajkd.2014.09.014>

35. Mayer O, Jr., Seidlerova J, Vanek J, Karnosova P, Bruthans J, Filipovsky J, Wohlfahrt P, Cifkova R, Windrichova J, Knapen MH, Drummen NE, Vermeer C (2016) The abnormal status of uncarboxylated matrix Gla protein species represents an additional mortality risk in heart failure patients with vascular disease. *Int J Cardiol* 203:916-922.

<https://doi.org/10.1016/j.ijcard.2015.10.226>

36. Zwakenberg SR, van der Schouw YT, Vermeer C, Pasterkamp G, den Ruijter HM, Beulens JWJ (2018) Matrix Gla protein, plaque stability, and cardiovascular events in patients with severe atherosclerotic disease. *Cardiology* 141:32-36.

<https://doi.org/10.1159/000493006>.

37. Yeap BB, Chubb SA, Flicker L, McCaul KA, Ebeling PR, Hankey GJ, Beilby JP, Norman PE (2012) Associations of total osteocalcin with all-cause and cardiovascular mortality in older men. The Health In Men Study. *Osteoporos Int* 23:599-606. [https://doi.org/ 10.1007/s00198-011-1586-1](https://doi.org/10.1007/s00198-011-1586-1).
38. Yamashita T, Okano K, Tsuruta Y, Akiba T, Nitta K (2013) Serum osteocalcin levels are useful as a predictor of cardiovascular events in maintenance hemodialysis patients. *Int Urol Nephrol* 45:207-214. [https://doi.org/ 10.1007/s11255-012-0156-6](https://doi.org/10.1007/s11255-012-0156-6).
39. Holvik K, van Schoor NM, Eekhoff EM, den Heijer M, Deeg DJ, Lips P, de Jongh R (2014) Plasma osteocalcin levels as a predictor of cardiovascular disease in older men and women: a population-based cohort study. *Eur J Endocrinol* 171:161-170. [https://doi.org/ 10.1530/eje-13-1044](https://doi.org/10.1530/eje-13-1044).
40. Hwang YC, Kang M, Cho IJ, Jeong IK, Ahn KJ, Chung HY, Lee MK (2015) Association between the circulating total osteocalcin level and the development of cardiovascular disease in middle-aged men: a mean 8.7-year longitudinal follow-up study. *J Atheroscler Thromb* 22:136-143. [https://doi.org/ 10.5551/jat.25718](https://doi.org/10.5551/jat.25718).
41. Miyake H, Kanazawa I, Sugimoto T (2018) Association of bone mineral density, bone turnover markers, and vertebral fractures with all-cause mortality in type 2 diabetes mellitus. *Calcif Tissue Int* 102:1-13. [https://doi.org/ 10.1007/s00223-017-0324-x](https://doi.org/10.1007/s00223-017-0324-x).
42. Zwakenberg SR, van der Schouw YT, Schalkwijk CG, Spijkerman AMW, Beulens JWJ (2018) Bone markers and cardiovascular risk in type 2 diabetes patients. *Cardiovasc Diabetol* 17:45. [https://doi.org/ 10.1186/s12933-018-0691-2](https://doi.org/10.1186/s12933-018-0691-2).

43. Cheung CL, Sahni S, Cheung BM, Sing CW, Wong IC (2015) Vitamin K intake and mortality in people with chronic kidney disease from NHANES III. *Clin Nutr* 34 (2):235-240. <https://doi.org/10.1016/j.clnu.2014.03.011>
44. Liu YP, Gu YM, Thijs L, Knapen MH, Salvi E, Citterio L, Petit T, Carpini SD, Zhang Z, Jacobs L, Jin Y, Barlassina C, Manunta P, Kuznetsova T, Verhamme P, Struijker-Boudier HA, Cusi D, Vermeer C, Staessen JA (2015) Inactive matrix Gla protein is causally related to adverse health outcomes: a Mendelian randomization study in a Flemish population. *Hypertension* 65 (2):463-470. <https://doi.org/10.1161/hypertensionaha.114.04494>
45. Riphagen IJ, Keyzer CA, Drummen NEA, de Borst MH, Beulens JWJ, Gansevoort RT, Geleijnse JM, Muskiet FAJ, Navis G, Visser ST, Vermeer C, Kema IP, Bakker SJL (2017) Prevalence and effects of functional vitamin K insufficiency: the PREVEND Study. *Nutrients* 9 (12):1334. <https://doi.org/10.3390/nu9121334>
46. Shea MK, Booth SL, Weiner DE, Brinkley TE, Kanaya AM, Murphy RA, Simonsick EM, Wassel CL, Vermeer C, Kritchevsky SB (2017) Circulating vitamin K is inversely associated with incident cardiovascular disease risk among those treated for hypertension in the Health, Aging, and Body Composition Study (Health ABC). *J Nutr* 147 (5):888-895. <https://doi.org/10.1161/strokeaha.117.01720610.3945/jn.117.249375>
47. Guo J, Astrup A, Lovegrove JA, Gijsbers L, Givens DI, Soedamah-Muthu SS (2017) Milk and dairy consumption and risk of cardiovascular diseases and all-cause mortality: dose-response meta-analysis of prospective cohort studies. *Eur J Epidemiol*

32:269-287. [https://doi.org/ 10.1007/s10654-017-0243-1](https://doi.org/10.1007/s10654-017-0243-1).

48. Rong Y, Chen L, Zhu T, Song Y, Yu M, Shan Z, Sands A, Hu FB, Liu L (2013) Egg consumption and risk of coronary heart disease and stroke: dose-response meta-analysis of prospective cohort studies. *BMJ* 346:e8539. [https://doi.org/ 10.1136/bmj.e8539](https://doi.org/10.1136/bmj.e8539).

49. Bechthold A, Boeing H, Schwedhelm C, Hoffmann G, Knuppel S, Iqbal K, De Henauw S, Michels N, Devleeschauwer B, Schlesinger S, Schwingshackl L (2017) Food groups and risk of coronary heart disease, stroke and heart failure: a systematic review and dose-response meta-analysis of prospective studies. *Crit Rev Food Sci Nutr*:1-20. [https://doi.org/ 10.1080/10408398.2017.1392288](https://doi.org/10.1080/10408398.2017.1392288).

50. Holick CN, Michaud DS, Stolzenberg-Solomon R, Mayne ST, Pietinen P, Taylor PR, Virtamo J, Albanes D (2002) Dietary carotenoids, serum beta-carotene, and retinol and risk of lung cancer in the alpha-tocopherol, beta-carotene cohort study. *Am J Epidemiol* 156 (6):536-547

51. Dietary Assessment Primer. Food frequency questionnaire at a Glance. National Cancer Institute, National Institutes of Health. 2016. Available from: <https://dietassessmentprimer.cancer.gov/profiles/questionnaire/> (cited 1 June 2018).

52. Lawlor DA, Smith GD, Bruckdorfer KR, Kundu D, Ebrahim S (2004) Those confounded vitamins: what can we learn from the differences between observational versus randomised trial evidence? *Lancet* 363 (9422):1724-1727. [https://doi.org/10.1016/s0140-6736\(04\)16260-0](https://doi.org/10.1016/s0140-6736(04)16260-0)

53. Pan A, Chen M, Chowdhury R, Wu JH, Sun Q, Campos H, Mozaffarian D, Hu FB

(2012) alpha-Linolenic acid and risk of cardiovascular disease: a systematic review and meta-analysis. *Am J Clin Nutr* 96 (6):1262-1273.

<https://doi.org/10.3945/ajcn.112.044040>

54. Jones KS, Bluck LJ, Wang LY, Coward WA (2008) A stable isotope method for the simultaneous measurement of vitamin K1 (phylloquinone) kinetics and absorption.

Eur J Clin Nutr 62 (11):1273-1281. <https://doi.org/10.1038/sj.ejcn.1602859>

55. van Ballegooijen AJ, Beulens JW (2017) The role of vitamin K status in cardiovascular health: evidence from observational and clinical studies. *Curr Nutr Rep*

6:197-205. <https://doi.org/10.1007/s13668-017-0208-8>.

56. EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies),

Turck D, Bresson JL, Burlingame B, Dean T, Fairweather-Tait S, Heinonen M,

Hirsch-Ernst KI, Mangelsdorf I, McArdle HJ, Naska A, Nowicka G, Pentieva K, Sanz

Y, Siani A, Sjodin A, Stern M, Tome D, Van Loveren H, Vinceti M, Willatts P,

Lamberg-Allardt C, Przyrembel H, Tetens I, Dumas C, Fabiani L, Ioannidou S,

Neuhauser-Berthold M, Nutr EPDP (2017) Scientific Opinion on the dietary reference values for vitamin K. *EFSA J* 15(5):4780, 78 pp.

<https://doi.org/10.2903/j.efsa.2017.4780>.

57. Shea MK, O'Donnell CJ, Hoffmann U, Dallal GE, Dawson-Hughes B, Ordovas

JM, Price PA, Williamson MK, Booth SL (2009) Vitamin K supplementation and

progression of coronary artery calcium in older men and women. *Am J Clin Nutr*. 89

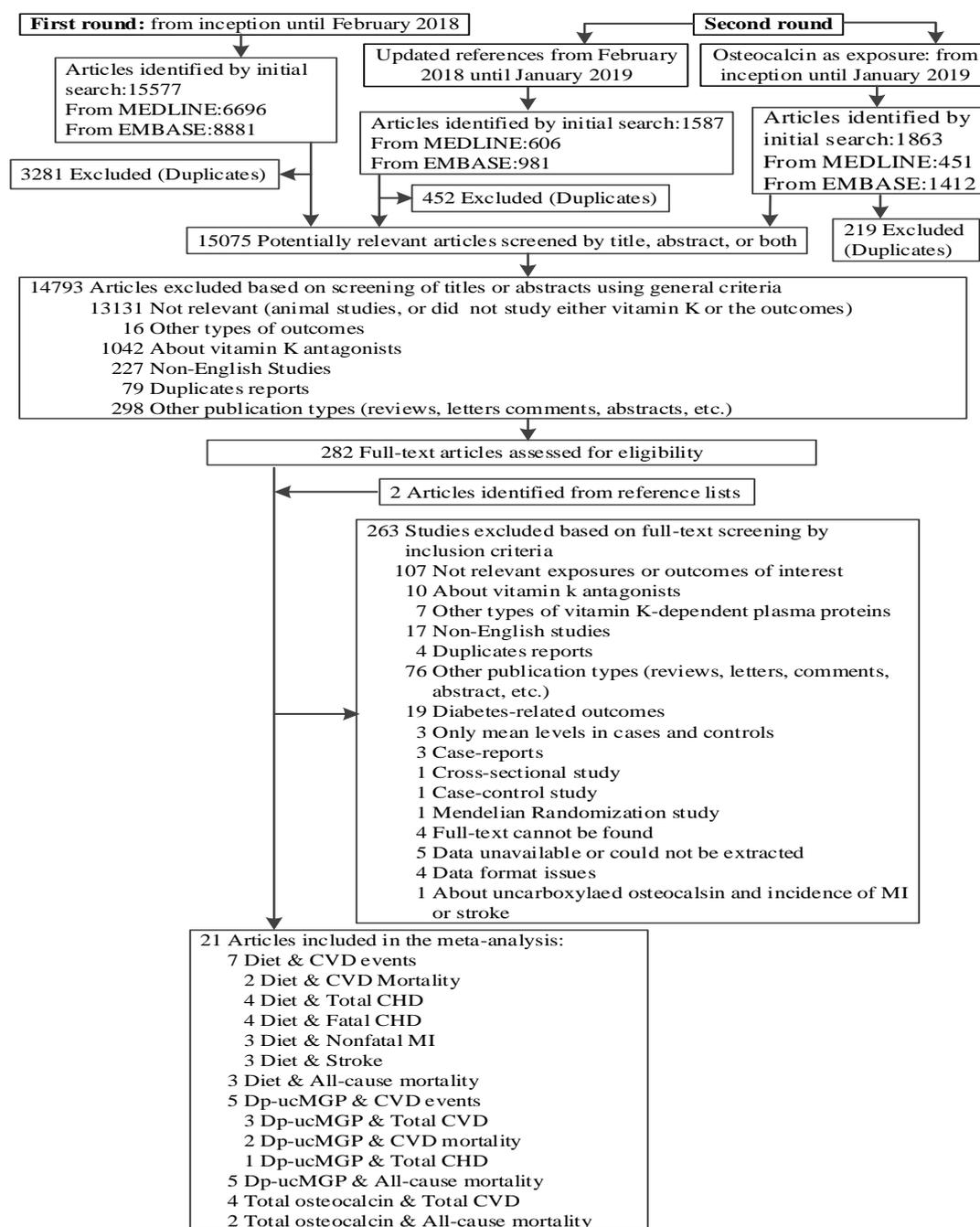
(6):1799-1807. <https://doi.org/10.3945/ajcn.2008.27338>

58. Knapen MH, Braam LA, Drummen NE, Bekers O, Hoeks AP, Vermeer C (2015)

- Menaquinone-7 supplementation improves arterial stiffness in healthy postmenopausal women. A double-blind randomised clinical trial. *Thromb Haemost* 113 (5):1135-1144. <https://doi.org/10.1160/TH14-08-0675>
59. Schurgers LJ, Uitto J, Reutelingsperger CP (2013) Vitamin K-dependent carboxylation of matrix Gla-protein: a crucial switch to control ectopic mineralization. *Trends Mol Med* 19 (4):217-226. <https://doi.org/10.1016/j.molmed.2012.12.008>
60. Cranenburg EC, Schurgers LJ, Vermeer C (2007) Vitamin K: the coagulation vitamin that became omnipotent. *Thromb Haemost* 98 (1):120-125
61. Spronk HM, Soute BA, Schurgers LJ, Thijssen HH, De Mey JG, Vermeer C (2003) Tissue-specific utilization of menaquinone-4 results in the prevention of arterial calcification in warfarin-treated rats. *J Vasc Res* 40 (6):531-537. <https://doi.org/10.1159/000075344>
62. Tsugawa N (2015) Cardiovascular diseases and fat soluble vitamins: vitamin D and vitamin K. *J Nutr Sci Vitaminol (Tokyo)* 61 Suppl:S170-172. <https://doi.org/10.3177/jnsv.61.S170>

Figure legends

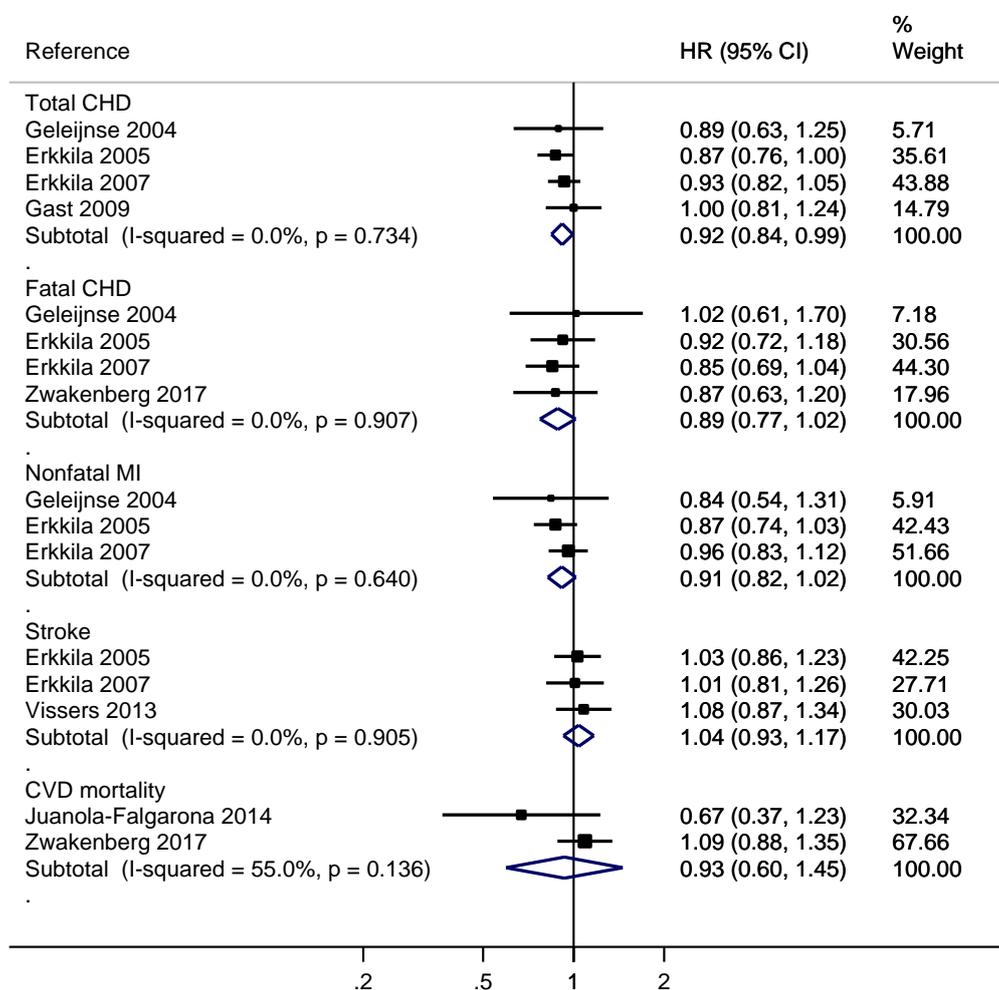
Fig. 1. Flowchart of diagram of the meta-analysis ¹



¹ We updated the articles from February 2018 to January 2019 and added “osteocalcin” as exposure (from inception until January 2019) in the second round.

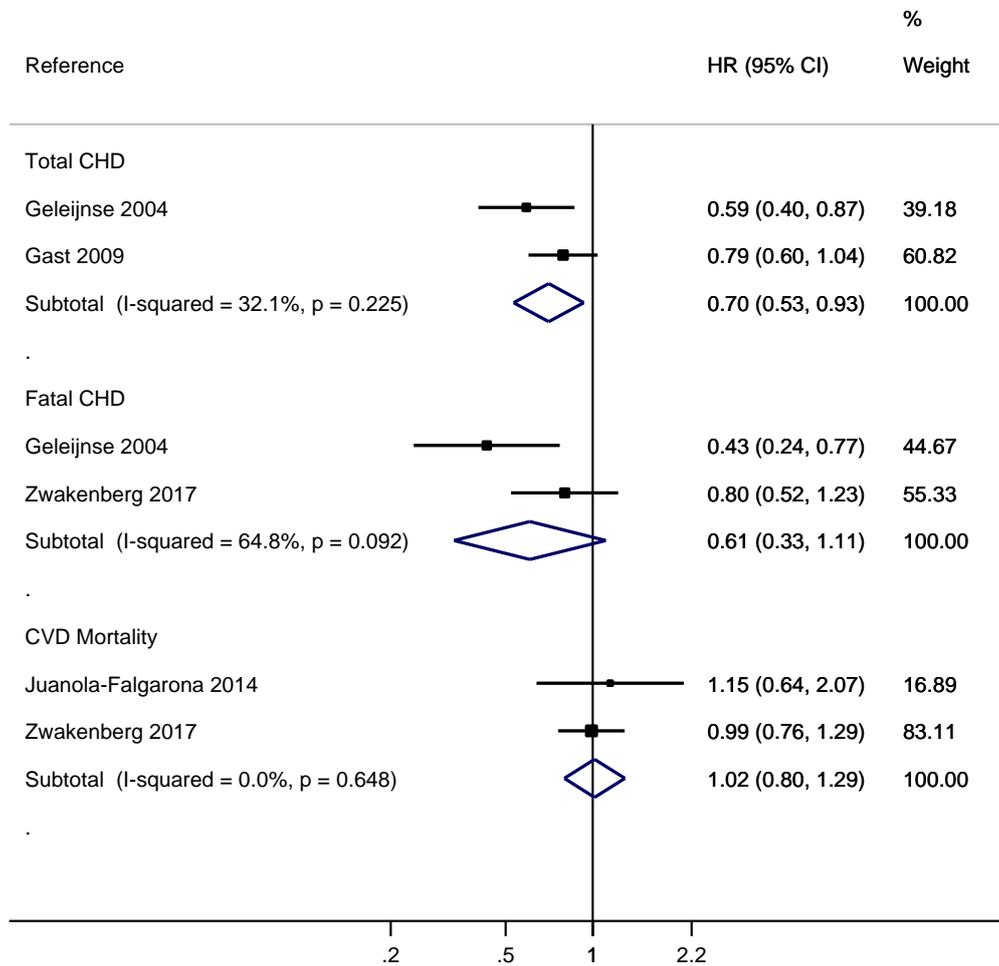
CHD, coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction.

Fig. 2. Association between dietary intake of phylloquinone and CVD risk: stratified by specific disease outcomes ¹



¹ The hazard ratios (HRs) were pooled by using random-effects meta-analysis. CHD, coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction.

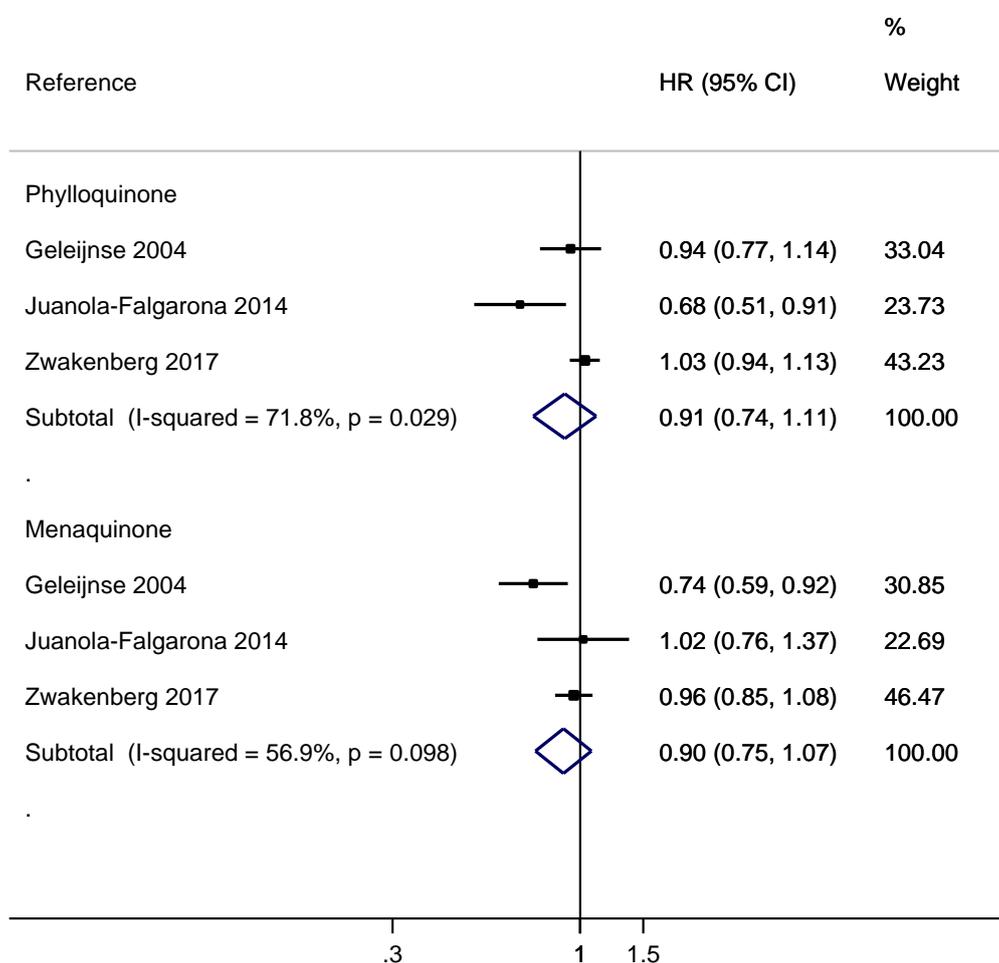
Fig. 3. Association between dietary intake of menaquinone and CVD risk: stratified by specific disease outcomes ¹



¹ The hazard ratios (HRs) were pooled by using random-effects meta-analysis. CHD, coronary heart disease; CVD, cardiovascular disease.

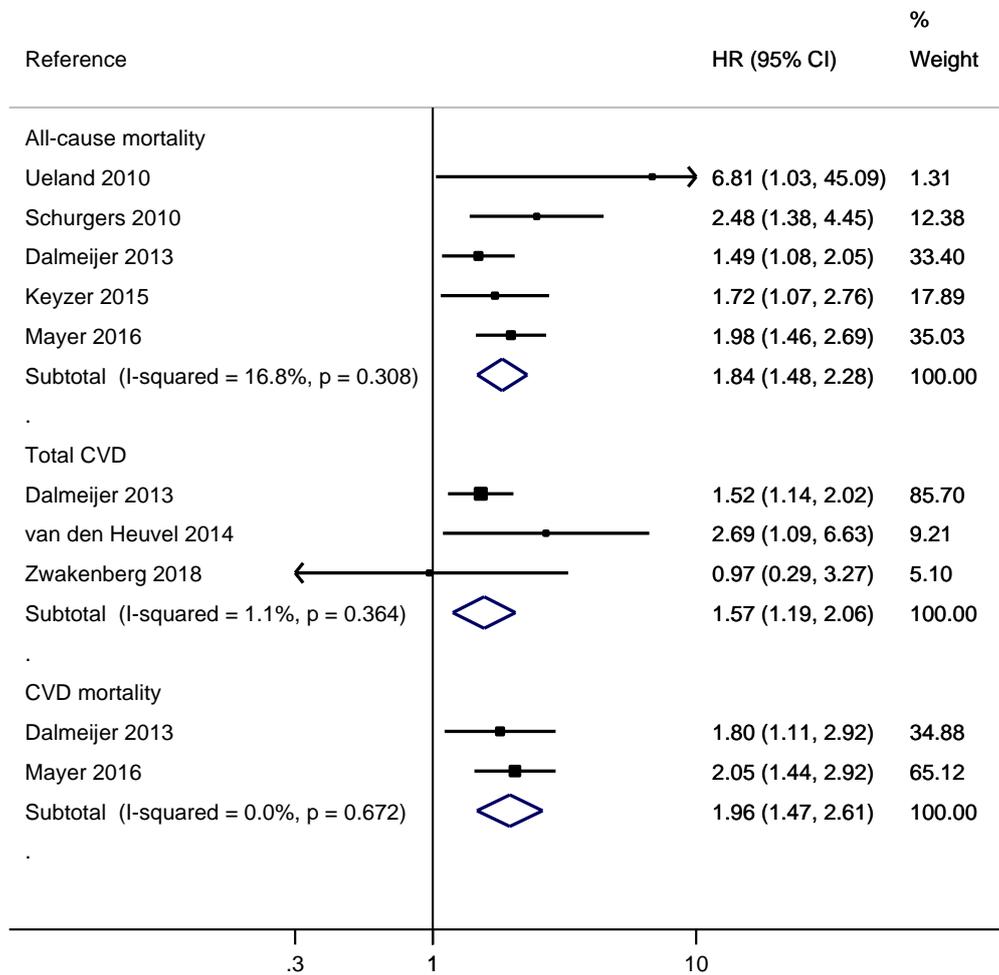
Fig. 4. Associations of dietary vitamin K consumption with risk of all-cause mortality

1



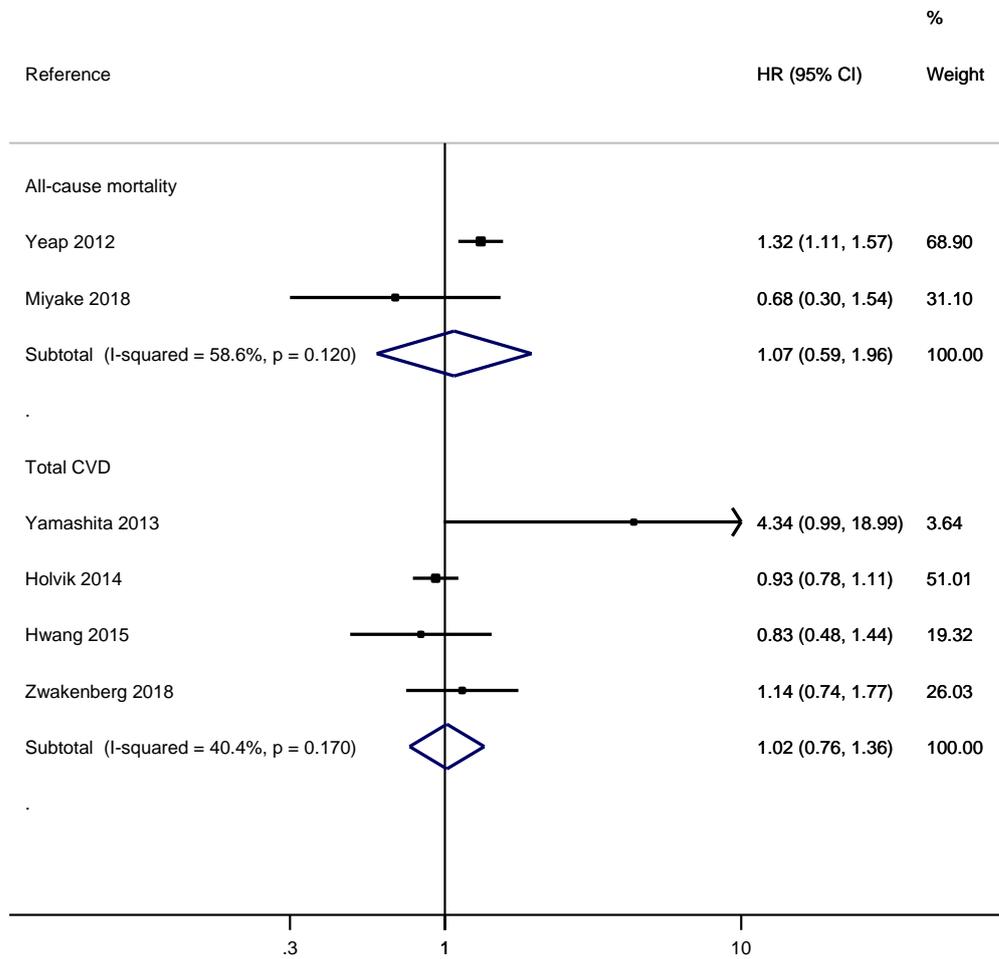
¹ The hazard ratios (HRs) were pooled by using random-effects meta-analysis.

Fig. 5. Associations of plasma dp-ucMGP concentration with risk of all-cause mortality and CVD events ¹



¹ The hazard ratios (HRs) were pooled by using random-effects meta-analysis. CVD, cardiovascular disease; dp-ucMGP, desphospho-uncarboxylated MGP.

Fig. 6. Associations of circulating total osteocalcin concentration with risk of all-cause mortality and total CVD ¹



¹ The hazard ratios (HRs) were pooled by using random-effects meta-analysis. CVD, cardiovascular disease.