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

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Author contributions

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

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Conflict of interest

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Abstract

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

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

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

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

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

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

Introduction

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

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

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

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

Methods

Search strategy

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

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

Study selection

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

Data extraction and quality assessment

The following information from each study was independently extracted by two

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

Statistical analysis

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

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

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

Results

Literature search

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

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

Included study characteristics

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

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

Dietary vitamin K with CVD events and all-cause mortality

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

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

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

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

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

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

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

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

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

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

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

were above 557 pmol/L.

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

Discussion

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

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

Higher plasma dp-ucMGP concentration has been consistently reported to be associated with increased risks of all-cause mortality in several original studies [29-31, 34, 35]. Empirically, target biomarker measured in plasma may provide more objective nutritional 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.

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

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

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

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

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

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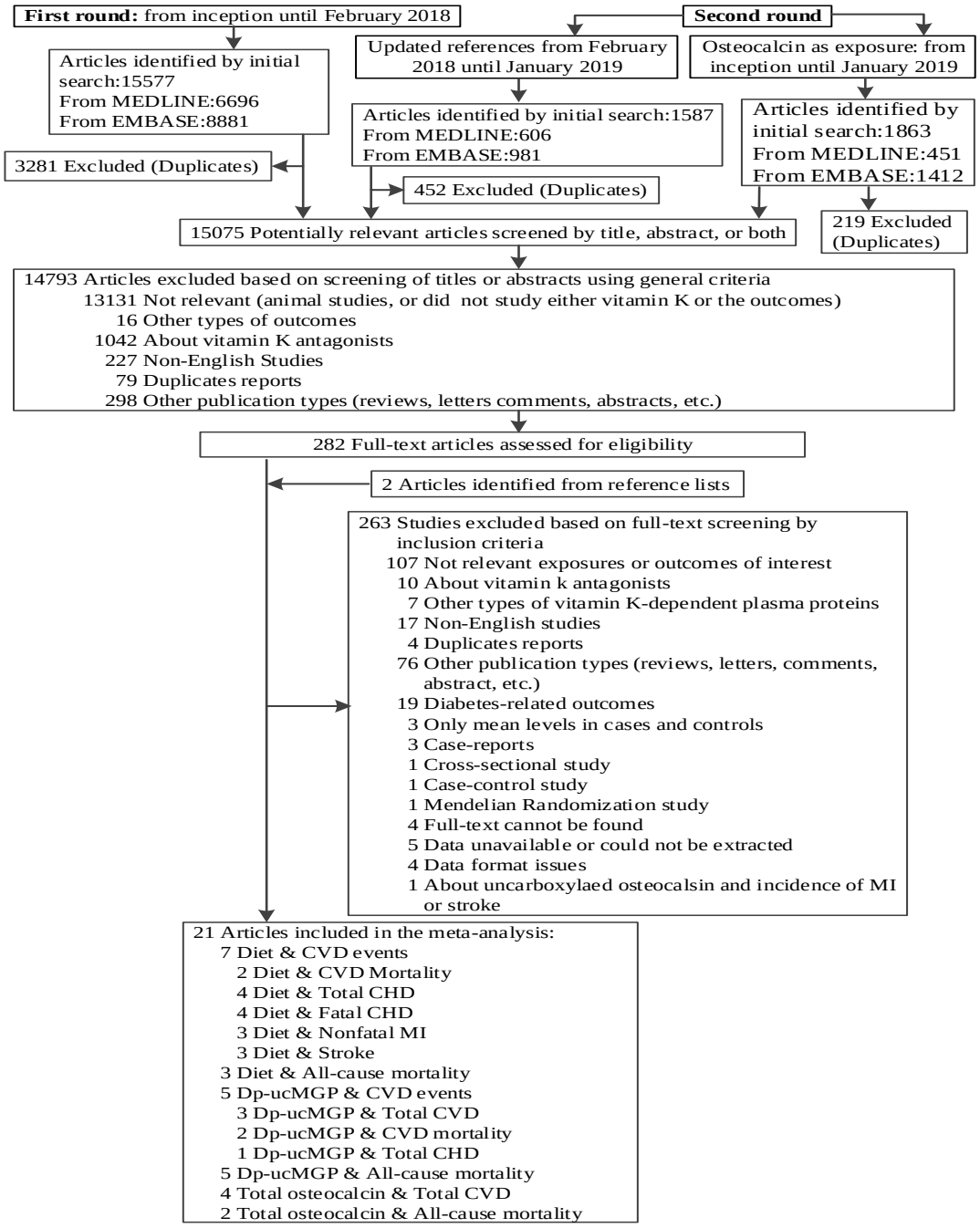
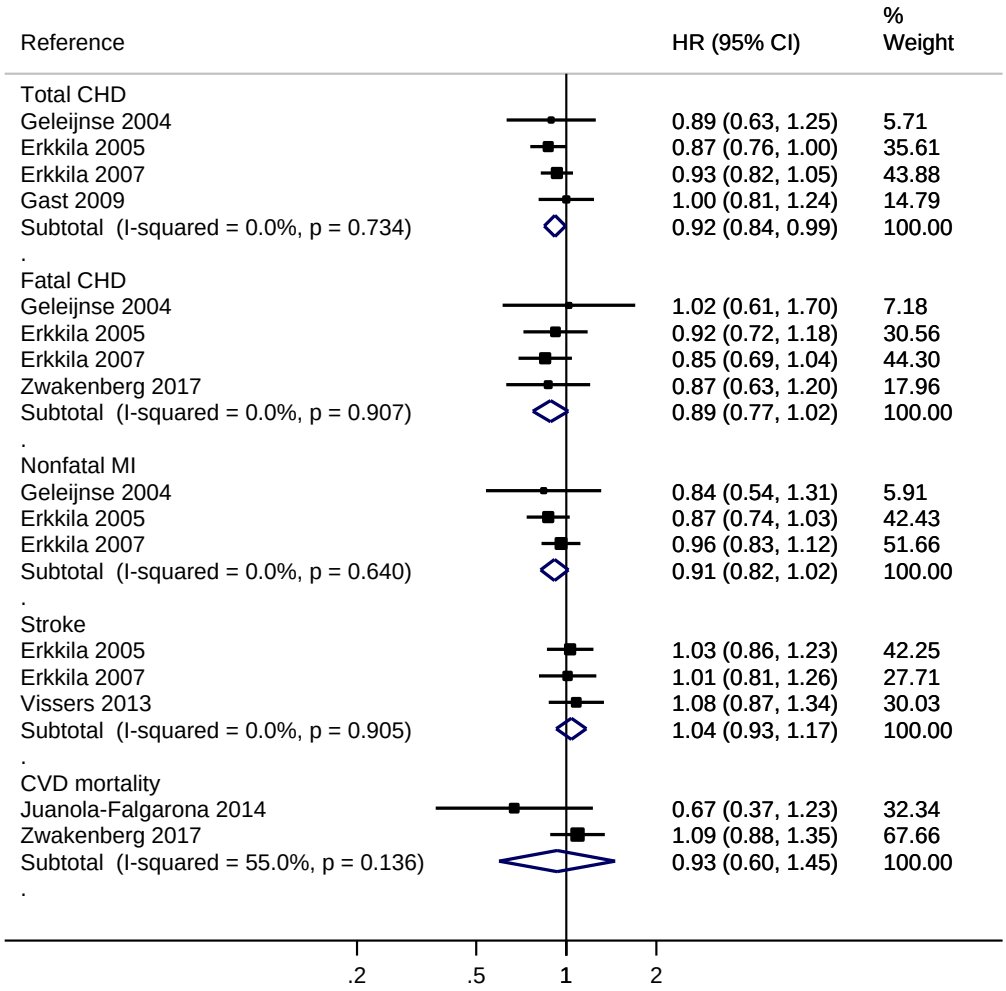
Figure legends

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



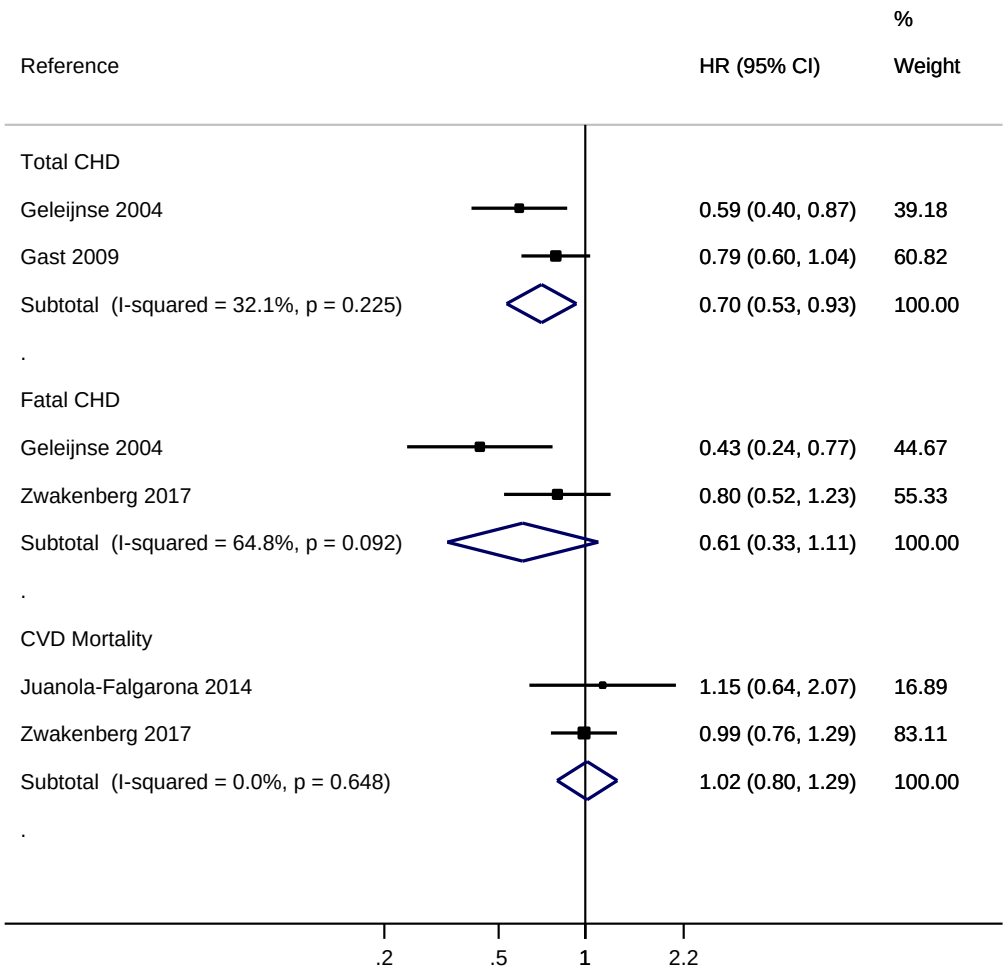
[1] We updated the articles from February 2018 to January 2019 and added "osteocalcin" as exposure (from inception until January 2019) in the second round. CHD, coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction.

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



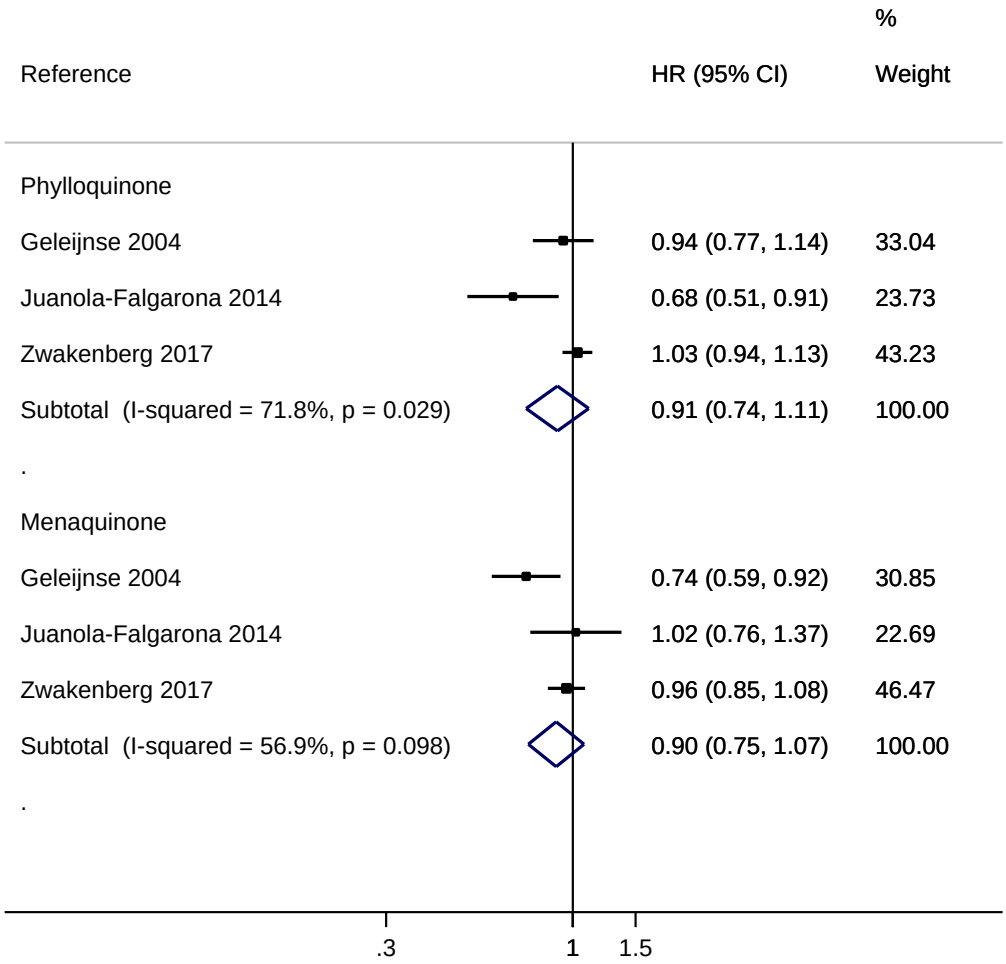
[1] The hazard ratios (HRs) were pooled by using random-effects meta-analysis. CHD, coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction.

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



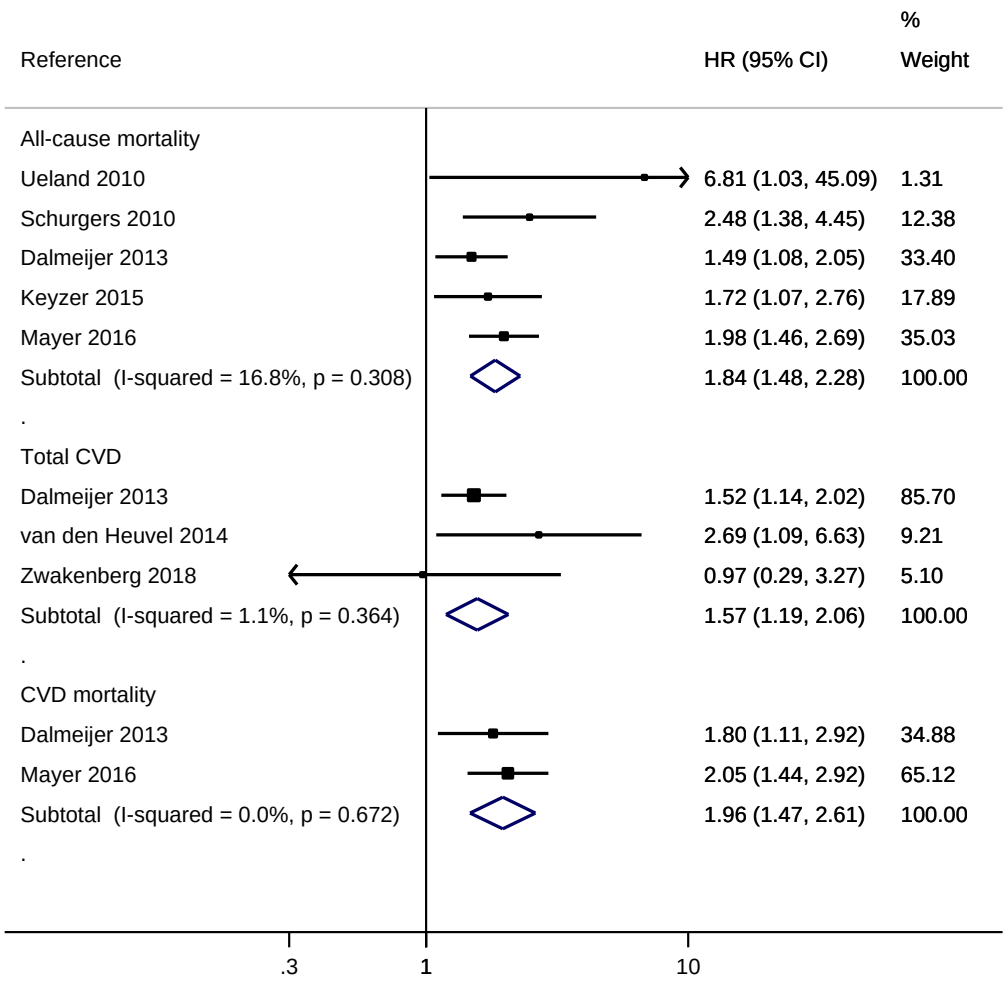
[1] The hazard ratios (HRs) were pooled by using random-effects meta-analysis. CHD, coronary heart disease; CVD, cardiovascular disease.

Fig. 4. Associations of dietary vitamin K consumption with risk of all-cause mortality [1]



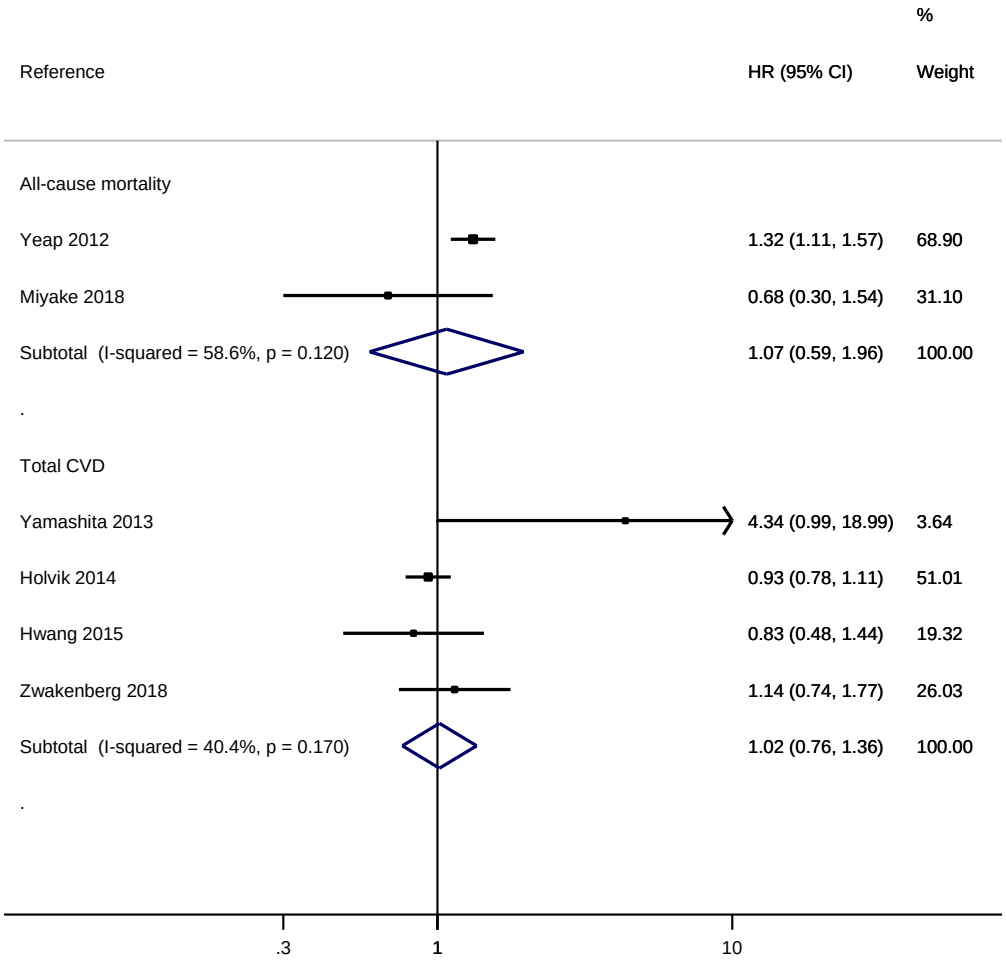
[1] The hazard ratios (HRs) were pooled by using random-effects meta-analysis.

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.