## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | The association of dietary vitamin K and risk of coronary heart disease in middle-age adults. The Hordaland Health Study cohort. |
| **AUTHORS** | Haugsgjerd, Teresa; Egeland Hovda, Grace; Nygård, Ottar K.; Vinknes, Kathrine J.; Sulo, Gerhard; Lysne, Vegard; Igland, Jannicke; Tell, Grethe |

## VERSION 1 – REVIEW

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| **REVIEWER** | Chiara de Waure<br>University of Perugia |
| **REVIEW RETURNED** | 20-Dec-2019 |

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| **GENERAL COMMENTS** | The paper “Dietary vitamin K and risk of coronary heart disease in the prospective Hordaland Health Study” addresses the role of vitamin K in CHD analysing data from a longitudinal study and national registries. The methodology is robust, but the main pitfall of the paper is represented by the lack of the reassessment of vitamin K intake and other CHD risk factors during the follow up time. This impairs results in my opinion and should be further elaborated as limit and in terms of validity of results. Furthermore, there are further comments as follows:<br>1. Exclusion criteria should be reported more clearly and more details about the methods used for their assessment should be reported. For example, Authors correctly excluded people with CHD at baseline, but how was that point assessed?<br>2. The development and choice of the multivariable models is not clear. I would select only one model considering all the potential confounding factors. Only a fully adjusted model would be able to provide the most valid estimation of the contribution of vitamin K intake to the incidence of CHD. In the case of effect modification, I would suggest reporting stratified data. |

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| **REVIEWER** | Houston, Mark<br>Vanderbilt University |
| **REVIEW RETURNED** | 11-Jan-2020 |

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| **GENERAL COMMENTS** | FFQ are not good ways to determine a nutritional outcome, but generates a hypothesis that requires more studies. Also Vit K 1 and K2 7 and K2 4 levels must be measured in any study to accurately demonstrate a cause and effect. In addition the quality of the dietary intake and the dietary supplement of Vit K must be verified. I would accept the paper with these limitations and hope others will do better with the methods. |

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| **REVIEWER** | Ehab S Eshak<br>Osaka University Japan |

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| | Minia University Egypt |
| **REVIEW RETURNED** | 20-Jan-2020 |

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| **GENERAL COMMENTS** | In their follow-up study for a mean 10-year period of 2987 men and women from Norway, the authors found significant inverse association between dietary vitamin K2 consumption and risk of coronary heart disease (CHD), but not for dietary intakes of vitamin K1. However, the association between vitamin K2 and risk of CHD lost its statistical significance after controlling for dietary intakes calcium and fiber.<br>Although the topic is really of clinical and epidemiological importance and showed interesting results; however, the authors appeared selective in presenting their findings.<br>The authors should not be selective to present only statistically significant data and directing the story to the statistically significant association observed after controlling for selected variables, especially with the use of invalidated FFQ intakes. It is obvious that vitamin K2 rather than K1 could have some association with the risk of CHD; however, the associations with vitamin K2 needs further assessment.<br><br>My comments can be summarized as<br>A- Introduction<br>1- Lines 82 to 90, the paragraph about GLa-containing proteins and its use for showing mechanisms to associate with CHD needs rewriting in a clear way.<br>2- Lines 89-90 “Both medial and intimal calcification, and both forms of calcification, have been shown when treated with vitamin K antagonists”. What did the authors refer to by when treated and by have been shown?<br>3- Please give reference to this statement “Given the limited number of studies on humans and the fact that sources and intake of 100 vitamin K differs between countries”.<br>4- English editing by a native is recommended;<br>Examples: how come smokers were classified as non-smokers (line 170), Residual where then (line 184), etc…<br>B- Methods<br>1- On what basis 10µg increments were used in the continuous analyses? Do 10µg changes in the dietary intake lead to a clinical difference? Why not using a standardized method like one standard deviation increment of each of vitamin K1 and vitamin K2 intakes?<br>2- Lines 198 to 205, the used continuous covariates were added into the model in what state? I.e., dummy variables for categories (what were the categories?) or continuous variables?<br>3- If meat and egg besides cheese were the main sources of vitamin K2 in this research, and accordingly the authors adjusted in supplementary analyses for SFA and calcium intakes, how about vitamin E intake and iron?<br>4- Similarly, vegetables and fruit were the main sources of vitamin K1 in this research, and accordingly the authors adjusted in supplementary analyses for fiber and folate intakes, how about vitamin C intake and potassium?<br>5- Missing data. The descriptions are confusing (excluded or imputed or …): -<br>In line 120-121 “23 participants (4 men and 19 121 women) were excluded due to missing information”. missing information on what?<br>In line 210 “Missing data were handled with listwise deletion”. How many? And what variables? |

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| | In lines 256-259 “Due to missing values (2.1% for 257 smoking habits, 0.8% for education and 5.2% for physical activity), multivariable-adjusted analyses included 2753 (1190 men and 1563 women) participants and 98 CHD events.”<br><br>How exactly did the authors handle missing data on exposure, outcome and covariates?<br>C. Results<br>1- Although the p-trends were statistically significant in tables 1 and 2; however, it is obvious that only the highest intake quartile Q4 (sometimes Q3 and Q4) are showing the described difference in text (lines 235 to 253). In most cases where a description of increasing level of covariates across quartiles of vitamin K was given, Q2 and Q3 show decreasing levels, while only Q4 shows the increment and vice versa for a description of decreasing levels of some other variables.<br>*- The associations in tables 1 and 2 seem to have taken U or inverted U shapes.<br>*- P-trend in some variables are highly significant, where a real absolute difference is not shown in the presented figures across the quartiles.<br>2- Why did the authors mention 60 deaths from other causes in line 259. These subjects are supposed to be censored at time of death? Is not it? Please describe the person-year calculation method and censoring in details.<br>3-Calculating the numbers and percentages given in lines 255 to 259 shows inconsistency.<br>*Even if the missing data have no overlapping, then the total excluded subjects should equal to 8.1 % of the 2987 participants; while the authors actually deleted 3.8% to reach 2753 subjects in the multivariable analysis.<br>*Meanwhile, a footnote under table 3 should indicate that multivariable analyses were based on a reduced number of participants and cases, because the tables show only the original number of 112 cases not 98 cases.<br>Regarding this important point I have two inquiries<br>1- Why did the authors exclude participants with missing data on smoking, education and physical activities? The three variables are categorical and a dummy variable representing the missing group of subjects can be added to the model.<br>2- By these exclusions, the authors had excluded 12.5% of the total CHD cases, which is a large proportion to be lost just due to missing covariates. The results could have been changed if these cases were included in the multivariable model.<br>Again, I advise the authors not be selective in presenting the data, those participants and CHD cases exclusions should be discussed, in which quartiles were most of them?<br><br>4-Most importantly is to show in tables (may be by adding another model in table 2) how adjusting for dietary SFA and calcium rendered the association between vitamin K2 and risk of CHD statistically insignificant.<br>What will be the HR (95%CI, p-trend) after further adjusting for dietary vitamin E and iron?<br>What were the correlation coefficients between vitamin K2, SFA and calcium?<br>Were SFA and calcium just strong confounding factors or they were effect modifiers in the associations between vitamin K2 and risk of CHD? Such results and discussion of the findings are important to improve the quality of the study. |

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| | 7-Why did the author show the penalized spline figure for model 1, but not model 2 or for a model adjusted for the other variables in supplementary analyses?<br>D. Discussion<br>1- Discussion should include the findings of the suggested analyses.<br>2-The authors should try to justify the discrepancy of their findings with those from previous studies. examples: the significant association with vitamin K1 in reference 20.<br>The null associations with either vitamin K1 and K2 in reference 19.<br>Also, a neutral discussion is recommended. For example, while showing a systematic review suggesting vitamin K supplements reduce vascular calcification (reference 42), there are other opposite findings that should be addressed. One randomized, double-blind clinical trial examined the effect of phylloquinone supplementation for 3 years and concluded no significant difference in coronary artery calcification between the treatment and control groups. Shea MK, O'Donnell CJ, Hoffmann U, Dallal GE, Dawson-Hughes B, Ordovas JM, et al. Vitamin K supplementation and progression of coronary artery calcium in older men and women. Am J Clin Nutr 2009;89:1799-807.<br>Findings of other clinical trials support the results of the authors Knapen MH, Braam LA, Drummen NE, Bekers O, Hoeks AP, Vermeer C. Menaquinone-7 supplementation improves arterial stiffness in healthy postmenopausal women: double-blind randomised clinical trial. Thromb Haemost 2015;113(5):1135–44.<br>Mansour AG, Hariri E, Daaboul Y, Korjian S, El Alam A, Protogerou AD, Kilany H, Karam A, Stephan A, Bahous SA. Vitamin K2 supplementation and arterial stiffness among renal transplant recipients—a single-arm, single-center clinical trial. J Am Soc Hypertens 2017;11(9):589–97. |

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| **REVIEWER** | Otto Mayer<br>Charles University, Medical Faculty Pilsen, Czech Republic |
| **REVIEW RETURNED** | 20-Jan-2020 |

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| **GENERAL COMMENTS** | The manuscript presents prospective follow-up study, based on general population sample and dealing with cardiovascular risk of K vitamins. Generally, there are no methodological problems, the analysis is adequately performed and manuscript well written. I have only two small suggestions: 1. it will be nice to describe briefly the methodology of selection of original Hordaland cohort (incl. reference); 2. power calculation should be mentioned in relevant section of Methods |

## VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Chiara de Waure

Institution and Country: University of Perugia

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
The paper “Dietary vitamin K and risk of coronary heart disease in the prospective Hordaland Health Study” addresses the role of vitamin K in CHD analysing data from a longitudinal study and national registries. The methodology is robust, but the main pitfall of the paper is represented by the lack of the reassessment of vitamin K intake and other CHD risk factors during the follow up time. This impairs results in my opinion and should be further elaborated as limit and in terms of validity of results.

*Response: This is mentioned under strengths and limitations (lines 319-321).*

Furthermore, there are further comments as follows:
1. Exclusion criteria should be reported more clearly and more details about the methods used for their assessment should be reported. For example, Authors correctly excluded people with CHD at baseline, but how was that point assessed?

*Response: The exclusion criteria are now described more clearly in the methods section (lines 118-122).*

2. The development and choice of the multivariable models is not clear. I would select only one model considering all the potential confounding factors. Only a fully adjusted model would be able to provide the most valid estimation of the contribution of vitamin K intake to the incidence of CHD. In the case of effect modification, I would suggest reporting stratified data.

*Response: We have clarified the rationale for the variables chosen for the multivariable models (line 199 – 213) and added a third model to table 3 (on request from Reviewer 3). We prefer to provide a parsimonious model and then larger multivariable models which provide readers with the ability to see the magnitude and direction of coefficients from model to model. We did not observe any effect modifications when we compared models with and without an interaction term using likelihood-ratio test.*

Reviewer: 2
Reviewer Name: mark houston md
Institution and Country: hypertension institute  USA
Please state any competing interests or state ‘None declared’: none

Please leave your comments for the authors below
FFQ are not good ways to determine a nutritional outcome, but generates a hypothesis that requires more studies.  Also Vit K 1 and K2 7 and K2 4 levels must be measured in any study to accurately demonstrate a cause and effect.  In addition the quality of the dietary intake and the dietary

supplement of Vit K must be verified. I would accept the paper with these limitations and hope others will do better with the methods.

*Response: We mention these issues in the limitations section of the discussion.*

Reviewer: 3
Reviewer Name: Ehab S Eshak
Institution and Country: Osaka University Japan. Minia University Egypt.
Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below
In their follow-up study for a mean 10-year period of 2987 men and women from Norway, the authors found significant inverse association between dietary vitamin K2 consumption and risk of coronary heart disease (CHD), but not for dietary intakes of vitamin K1. However, the association between vitamin K2 and risk of CHD lost its statistical significance after controlling for dietary intakes calcium and fiber.
Although the topic is really of clinical and epidemiological importance and showed interesting results; however, the authors appeared selective in presenting their findings.
The authors should not be selective to present only statistically significant data and directing the story to the statistically significant association observed after controlling for selected variables, especially with the use of invalidated FFQ intakes. It is obvious that vitamin K2 rather than K1 could have some association with the risk of CHD; however, the associations with vitamin K2 needs further assessment.

*Response: Yes, we agree with the reviewer that our findings suggests that further research is needed regarding vitamin K2. We have modified the presentation of results which also highlight the non-significant findings.*

My comments can be summarized as
A- Introduction
1-Lines 82 to 90, the paragraph about GLa-containing proteins and its use for showing mechanisms to associate with CHD needs rewriting in a clear way.

*Response: We have revised the text and hopefully made this section clearer (lines 77 – 87).*

2-Lines 89-90 "Both medial and intimal calcification, and both forms of calcification, have been shown when treated with vitamin K antagonists". What did the authors refer to by when treated and by have been shown?

*Response: This sentence is revised (lines 83-85) and includes more details.*

3-Please give reference to this statement “Given the limited number of studies on humans and the fact that sources and intake of 100 vitamin K differs between countries”.

*Response: The text is revised and references are included (lines 96-97).*

4-English editing by a native is recommended;
Examples: how come smokers were classified as non-smokers (line 170), Residual where then (line 184), etc…

*Response: These misspellings have been corrected (lines 172-173 and 188) and a native English speaking researcher has edited the manuscript.*

B- Methods
1-On what basis 10µg increments were used in the continuous analyses? Do 10µg changes in the dietary intake lead to a clinical difference? Why not using a standardized method like one standard deviation increment of each of vitamin K1 and vitamin K2 intakes?

*Response: We understand your point; however, we prefer to keep the analyses based upon the 10 µg increments in dietary intake of vitamin K in the manuscript as it is more readily interpretable than 1 SD increments and allows comparisons to studies that also used 10 ug increments in their analyses (Gast et al 2009, Zwakenberg et al. 2017).*

2-Lines 198 to 205, the used continuous covariates were added into the model in what state? I.e., dummy variables for categories (what were the categories?) or continuous variables?

*Response: This is made clearer in the revised text (lines 199-213).*

3-If meat and egg besides cheese were the main sources of vitamin K2 in this research, and accordingly the authors adjusted in supplementary analyses for SFA and calcium intakes, how about vitamin E intake and iron?

*Response:*

| *Exposure* | *HR (95% CI)** |
|---|---|
| *Vitamin K2* | |
| *Q1* | *1 (ref)* |
| *Q2* | *0.83 (0.48 to 1.42)* |
| *Q3* | *0.84 (0.47 to 1.50)* |

| | |
|---|---|
| *Q4* | *0.59 (0.29 to 1.22)* |
| *P – trend[f]* | *0.179* |
| | |
| *Continuous, Per 10 µg* | *0.83 (0.52 to 1.32) p = 0.432* |

**Adjusted for age, sex, energy intake, physical activity, smoking habits, education, energy-adjusted SFA, calcium, vitamin E and iron.*

*When adjusting for vitamin E and iron in addition, the results hardly change compared to the results in Table 3, Model 3. We prefer not to include these adjustments since it does not add useful information.*

4-Similarly, vegetables and fruit were the main sources of vitamin K1 in this research, and accordingly the authors adjusted in supplementary analyses for fiber and folate intakes, how about vitamin C intake and potassium?

*Response: We have now conducted a supplemental analyses including vitamin C as a covariate. Again, results are not altered when compared to those of Table 3, Model 3. Unfortunately, we do not have data on potassium. However, as potassium sources include dietary sources of fiber and folate, potassium was likely indirectly adjusted for in the analyses.*

| *Exposure* | *HR (95% CI)* |
|---|---|
| *Vitamin K1* | |
| *Q1* | *1 (ref)* |
| *Q2* | *0.48 (0.26 to 0.89)* |
| *Q3* | *0.83 (0.49 to 1.41)* |
| *Q4* | *0.70 (0.38 to 1.30)* |
| *P – trend[f]* | *0.623* |
| | |
| *Continuous, Per 10 µg* | *0.99 (0.96 to 1.01) p = 0.279* |

**Adjusted for age, sex, energy intake, physical activity, smoking habits, education, energy-adjusted fiber, folate, vitamin C.*

5-Missing data. The descriptions are confusing (excluded or imputed or …): -
In line 120-121 “23 participants (4 men and 19 121 women) were excluded due to missing information”. missing information on what?

*Response: We have made it clearer whether we are referring to excluded or imputed (lines 118-122).*

In line 210 “Missing data were handled with listwise deletion”. How many? And what variables?
In lines 256-259 “Due to missing values (2.1% for 257 smoking habits, 0.8% for education and 5.2% for physical activity), multivariable-adjusted analyses included 2753 (1190 men and 1563 women) participants and 98 CHD events.”

How exactly did the authors handle missing data on exposure, outcome and covariates?

*Response: We have revised the text on listwise deletion (lines 218-219) and are now clearer about how we handle missing data throughout the manuscript.*
*We excluded 6 participants (2 men and 4 women) with missing information on intake of vitamin K (lines 123-124).*
*There were no participants missing outcomes as linkage to the CVDNOR project database assured complete follow-up (lines 313-314).*
*Missing data on covariates were handled with listwise deletion (lines 218-219, 271-275). Due to missing values (2.1% for smoking habits, 0.8% for education and 3.8% for physical activity), multivariable-adjusted analyses (Table 3, Model 2 and 3) included 6.5% fewer participants compared to the parsimonious model 1, yielding 2792 (1213 men and 1579 women) participants and 100 CHD events. In supplementary analyses missing values on physical activity, smoking and education were imputed using ordinal logistic regression as the imputation model in MICE (multiple imputation using chained equation) with 20 imputations (lines 218-225).*

C. Results
1- Although the p-trends were statistically significant in tables 1 and 2; however, it is obvious that only the highest intake quartile Q4 (sometimes Q3 and Q4) are showing the described difference in text (lines 235 to 253). In most cases where a description of increasing level of covariates across quartiles of vitamin K was given, Q2 and Q3 show decreasing levels, while only Q4 shows the increment and vice versa for a description of decreasing levels of some other variables.

*- The associations in tables 1 and 2 seem to have taken U or inverted U shapes.

*- P-trend in some variables are highly significant, where a real absolute difference is not shown in the presented figures across the quartiles.

*Response: Since each intake category contains approximately 750 participants, small variations in descriptive characteristics can produce significant trends. In addition, the trend-test for continuous characteristics evaluates the trend of the mean intake in each quartile, while we are reporting the median (25 percentile, 75 percentile) in each quartile. This may explain why some variables are highly significant, while a real absolute difference is not shown.*

2- Why did the authors mention 60 deaths from other causes in line 259. These subjects are supposed to be censored at time of death? Is not it? Please describe the person-year calculation method and censoring in details.

*Response: We agree that this information was unclear in the previous context. We have moved the sentence to lines 181-182, where it fits better to the context and where the method for censoring is described (lines 179-182). The small number of other deaths is important to report as it indicates that competing risk from other diseases would not to be a problem.*

3-Calculating the numbers and percentages given in lines 255 to 259 shows inconsistency.
*Even if the missing data have no overlapping, then the total excluded subjects should equal to 8.1 % of the 2987 participants; while the authors actually deleted 3.8% to reach 2753 subjects in the multivariable analysis.
*Meanwhile, a footnote under table 3 should indicate that multivariable analyses were based on a reduced number of participants and cases, because the tables show only the original number of 112 cases not 98 cases.

*Response: We apologize for the confusion. The text is clearer now (line 271-275). Since we have included a new covariate on physical activity with fewer missing values, the numbers presented have changed. We have also added a footnote under table 3 and mentioned the number of participants in the first row.*

Regarding this important point I have two inquiries
1- Why did the authors exclude participants with missing data on smoking, education and physical activities? The three variables are categorical and a dummy variable representing the missing group of subjects can be added to the model.

*Response: When adding a dummy variable representing the missing group of subjects (Missing indicator method), we consider all participants with missing information on the specific covariate as identical: an assumption which may not be correct. This may introduce unpredictable bias of the HR even with small percentages of missing values (Knol MJ, et al, Unpredictable bias when using the missing indicator method or complete case analysis for missing confounder values: an empirical example. Journal of Clinical Epidemiology 2010:63;728-736). Knol et al found that the missing indicator method gave an overestimation of the odds ratio when missing values were completely random, while it gave an under- or overestimation when missing values depended on observed values (Knol 2010).*
*We have made it clearer that we are referring to listwise deletion (complete case analysis) of missing in covariates, and also added a supplementary table where we handle the missing values with multiple imputation (lines 218-225, 271-275, 283-285 and 298-300).*

2-By these exclusions, the authors had excluded 12.5% of the total CHD cases, which is a large proportion to be lost just due to missing covariates. The results could have been changed if these cases were included in the multivariable model.
Again, I advise the authors not be selective in presenting the data, those participants and CHD cases exclusions should be discussed, in which quartiles were most of them?

*Response: After adding a new covariate on physical activity (with fewer missing values), we have excluded 10.7% of the total CHD cases in the main analyses. As stated above, we have also run supplementary analyses using multiple imputation for missing values on covariates.*

4-Most importantly is to show in tables (may be by adding another model in table 2) how adjusting for dietary SFA and calcium rendered the association between vitamin K2 and risk of CHD statistically insignificant.
What will be the HR (95%CI, p-trend) after further adjusting for dietary vitamin E and iron?
What were the correlation coefficients between vitamin K2, SFA and calcium?
Were SFA and calcium just strong confounding factors or they were effect modifiers in the associations between vitamin K2 and risk of CHD? Such results and discussion of the findings are important to improve the quality of the study.

*Response: The additional adjustments for dietary habits already mentioned in the manuscript are included as Model 3 in Table 3, and are now referred to in the abstract and result section (lines 282-283, 295-298). In terms of iron and vitamin E adjustment, see our response above to comment B3.*

| *Spearman correlation coefficients between vitamin K2, SFA and calcium* | | |
|---|---|---|
| | *Vitamin K2* | *Saturated fat* |
| *Saturated fat* | *0.55* | |
| *Calcium* | *0.35* | *0.17* |

*As shown in the table the correlation between SFA and K2 is high, as would be expected given the shared dietary sources of SFA and K2. Further, when evaluating VIF in the multivariable model (Table 3, Model 3), VIF is 1.55 for vitamin K2 when analyzing the trend through the quartiles. When evaluating the different quartiles of vitamin K2 intake, VIF ranges from 2.10 to 3.00, while for intake of SFA as an energy-adjusted continuous variable, VIF is 1.46.*
*There were no significant interactions between intake of energy-adjusted vitamin K2 with saturated fat ($p = 0.82$) or calcium ($p = 0.54$).*

7-Why did the author show the penalized spline figure for model 1, but not model 2 or for a model adjusted for the other variables in supplementary analyses?

*Response: We are now showing the figure for model 2.*

D. Discussion

1- Discussion should include the findings of the suggested analyses.

*Response: We have extended the discussion so that it covers the results in model 3 (lines 309-310, 352-356, 379-387). Due to word limitations (4000 words), we don't think the discussion can be larger (we already have 4167 words).*

2-The authors should try to justify the discrepancy of their findings with those from previous studies. examples: the significant association with vitamin K1 in reference 20.
The null associations with either vitamin K1 and K2 in reference 19.

*Response: We have included text related to the variability in study findings and potential explanations for discrepancies in results (lines 340-342, 346-348, 352-356, 358-361).*

Also, a neutral discussion is recommended. For example, while showing a systematic review suggesting vitamin K supplements reduce vascular calcification (reference 42), there are other opposite findings that should be addressed. One randomized, double-blind clinical trial examined the effect of phylloquinone supplementation for 3 years and concluded no significant difference in coronary artery calcification between the treatment and control groups. Shea MK, O'Donnell CJ, Hoffmann U, Dallal GE, Dawson-Hughes B, Ordovas JM, et al. Vitamin K supplementation and progression of coronary artery calcium in older men and women. Am J Clin Nutr 2009;89:1799-807.
Findings of other clinical trials support the results of the authors
Knapen MH, Braam LA, Drummen NE, Bekers O, Hoeks AP, Vermeer C. Menaquinone-7 supplementation improves arterial stiffness in healthy postmenopausal women: double-blind randomised clinical trial. Thromb Haemost 2015;113(5):1135–44.
Mansour AG, Hariri E, Daaboul Y, Korjian S, El Alam A, Protogerou AD, Kilany H, Karam A, Stephan A, Bahous SA. Vitamin K2 supplementation and arterial stiffness among renal transplant recipients—a single-arm, single-center clinical trial. J Am Soc Hypertens 2017;11(9):589–97.

*Response: We have included results from the study by Shea et al (lines 373-377). However, due to word limitations, we focus our text on epidemiological studies of dietary intake in healthy study participants and not on clinical trials.*

Reviewer: 4
Reviewer Name: Otto Mayer
Institution and Country: Charles University, Medical Faculty Pilsen, Czech Republic
Please state any competing interests or state 'None declared': none

Please leave your comments for the authors below

The manuscript presents prospective follow-up study, based on general population sample and dealing with cardiovascular risk of K vitamins. Generally, there are no methodological problems, the analysis is adequately performed and manuscript well written. I have only two small suggestions:
1. it will be nice to describe briefly the methodology of selection of original Hordaland cohort (incl. reference);

*Response:*
*This is now described (lines 105-107).*

2. power calculation should be mentioned in relevant section of Methods

*Response:*
*Our study represents a secondary analyses of a prospective cohort study. As other large community-based studies, the HUSK study was undertaken to examine a range of research topics and questions. Before the baseline examinations in 1997-99, power calculations were not performed for each research question, and over the years new research questions were posed.*

**VERSION 2 – REVIEW**

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| **REVIEWER** | Chiara de Waure<br>University of Perugia |
| **REVIEW RETURNED** | 02-Mar-2020 |

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| **GENERAL COMMENTS** | Authors have successfully answered to my previous comment |

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| **REVIEWER** | Ehab S Eshak<br>Osaka University, Japan<br>Minia Uinversity, Egypt |
| **REVIEW RETURNED** | 02-Mar-2020 |

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| **GENERAL COMMENTS** | The authors have responded adequately to the raised comments. I have no other comments. |