Coffee

No. 2023/02Ge, The Hague, February 7, 2023

Background document to the advisory report:
Dutch dietary guidelines for people with atherosclerotic cardiovascular disease
No. 2023/02e, The Hague, February 7, 2023

Health Council of the Netherlands

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1 Introduction

This background document belongs to the advisory report *Dutch dietary guidelines for people with atherosclerotic cardiovascular disease* (ASCVD).[1] It describes the methodology for the search, selection and evaluation of the literature regarding the relationship between coffee consumption and health outcomes in people with ASCVD. It also describes the scientific evidence on this topic and the conclusions that have been drawn by the council's Committee on Nutrition.

1.1 Definition of coffee

Coffee is a drink made of coffee beans, which naturally contains caffeine. Caffeine-free coffee, or decaffeinated coffee, also exists. It is produced by the use of water, organic solvents or steam, or through blocking the expression of genes encoding caffeine. The composition of coffee is furthermore dependent on the method of preparation, including the degree to which the coffee beans were roasted and whether the coffee was prepared using a filter or not. The latter is in particular relevant in the context of health, since the filter can remove the cholesterol-elevating compounds kahweol and cafestol.[2] Examples of filtered coffee are coffee pads, instant coffee and machine coffee based on liquid coffee concentrate. Examples of unfiltered coffee are cafetiere coffee, Greek coffee and Turkish coffee. Some types of coffee can be filtered or unfiltered depending on the machine, the type and amount of coffee, and the type of filter used. In the current evaluation of the literature on coffee consumption, the Committee aimed to consider, were possible, whether or not the consumed coffee was caffeinated or decaffeinated and what the brewing method was.

1.2 Coffee recommendations and intake in the Netherlands

The Health Council of the Netherlands included a guideline for coffee consumption in the *Dutch dietary guidelines 2015*, which is as follows: *'*Replace unfiltered coffee by filtered coffee'.*[3]*

Data from the Dutch National Food Consumption Survey (2012-2016) shows that the general Dutch population aged 19 to 79 years consumes on average 492 grammes of coffee daily.[4] This equals approximately 3.5 cups of coffee a day.[5] To what extend the coffee consumed was filtered or unfiltered is unknown.

2 Methodology

2.1 Questions

The Committee aimed to answer the following question: What is the relationship (effect or association) of relatively higher coffee consumption compared to no or relatively lower coffee consumption with health outcomes in people with ASCVD? In addition, the Committee aimed to evaluate whether the observed relationship of coffee consumption with health outcomes depends on whether the coffee was caffeinated or decaffeinated and whether the coffee was filtered or unfiltered.

2.2 Target group

The target group of the current advisory report is people with ASCVD. The Committee defines this group as people with clinically established coronary heart disease (CHD, consisting of acute coronary syndromes [myocardial infarction and unstable angina], stable angina and revascularisation procedures such as percutaneous coronary intervention [PCI] and coronary artery bypass grafting [CABG]), peripheral arterial disease (PAD) or cerebrovascular disease (consisting of stroke and transient ischemic attack). In the target population, atherosclerosis in the coronary arteries, aorta, iliac and femoral arteries, and cerebral arteries is the main underlying pathological process. Groups with a high risk (but no manifestation) of ASCVD, such as people with hypertension or elevated LDL cholesterol levels, fall outside this definition. Also, the target group of this advice does not include people with heart failure (except when those people also suffer from ASCVD). A detailed description of the target group of this advisory report is provided in the background document *Methodology for the evaluation of the evidence*.[6]

In the present background document, the Committee also considered studies performed in people with cardiovascular disease (CVD) in general (not further specified), under the assumption that the majority of this population will have ASCVD.

2.3 Nutritional topics

The Committee searched for studies into coffee consumption, which could be either caffeinated or decaffeinated coffee (or mixed) and filtered or unfiltered coffee (or mixed). The Committee also considered studies into caffeine intake from coffee, as long as the exposure concerned caffeine from coffee alone. In this case, the Committee assumed that caffeine intake was highly correlated with (caffeinated) coffee consumption. Studies in which the exposure was total caffeine, i.e., caffeine from various food sources besides coffee such as tea, chocolate or soft drinks, were excluded.

The Committee preferred to include studies in which coffee consumption was measured after the occurrence of the ASCVD event, and preferably at least 6 months after the event in order to capture the habitual post-event intake and long-term effects of this exposure, since people may change their dietary habits because of an ASCVD event. If this was not the case or if information on this topic was lacking, the Committee noted this as a limitation to the study.

2.4 Health outcomes

The Committee selected the following health outcomes for this advisory report (for which a motivation is provided in the background document *Methodology for the evaluation of the evidence*[6]*:*

- short-term surrogate outcomes:
  - body weight
  - systolic blood pressure
  - low-density lipoprotein (LDL) cholesterol
  - estimated glomerular filtration rate (eGFR)
  - glycated haemoglobin (HbA1c) and fasting blood glucose
- long-term health outcomes:
  - all-cause mortality
  - morbidity and/or mortality from total CVD, CHD, stroke (cerebrovascular disease), heart failure, atrial fibrillation, type 2 diabetes, chronic obstructive pulmonary diseases (COPD), total cancer, breast cancer, colorectal cancer, lung cancer, dementia, depression
  - subtypes of CHD, such as myocardial infarction (MI), angina pectoris and revascularisation procedures (i.e., coronary artery bypass surgery and percutaneous coronary intervention)

For cohort studies, the Committee included only studies in the above-described category named long-term health outcomes.

2.5 Selection and evaluation of the literature and drawing conclusions

A detailed description of the approach used by the Committee for selecting and evaluating the scientific literature is provided in the background document *Methodology for the evaluation of the evidence*.[6] In short, the Committee aimed to base its evaluation of scientific literature on systematic reviews (SRs), including meta-analyses (MAs), of randomised controlled trials (RCTs) and/or prospective cohort studies (i.e. prospective cohort studies, nested case-control studies and case-cohort studies) examining the relationship of coffee consumption with the above-mentioned health outcomes in people with ASCVD. To identify such publications, the Committee searched PubMed and Scopus in May 2021. Next, PubMed and Scopus were

searched for individual RCTs in August 2022. The search strategies specifications of the study selections are presented in Annex A.
The Committee aimed to present its findings and draw conclusions for the total group of people with ASCVD and organised per subtype of ASCVD, where possible.

2.5.1 Search and selection of studies

The Committee found two MAs of prospective cohort studies that addressed associations of coffee consumption with all-cause mortality, CVD mortality and/or the incidence of subtypes of CVD in people with a history of myocardial infarction (MI; Annex A).[7,8] Because the studies included in the MAs overlapped, one (the most recent; Ribeiro et al.[8]) MA was included in the Committee's evaluation.[8] In addition, the Committee identified one individual prospective cohort study through checking reference lists of the identified MAs.[9] This study examined associations of coffee consumption with all-cause mortality and CVD mortality in women with prior CVD. By searching PubMed for similar articles to the already found prospective cohort studies, two additional individual cohort studies were identified and selected by the Committee.[10,11] Moreover, one additional prospective cohort study relevant for the Committee's evaluation was selected via the literature search on another nutritional topic for the current advisory report (alcohol).[12] During the search for individual RCTs one RCT was found that investigated the effect of coffee versus decaffeinated coffee on CVD mortality and CVD events in people who experienced a MI.[13] The study found no significant differences between the groups on the health outcomes. One RCT provides too little evidence to base conclusions on for the current advisory report and therefore this study was not further described in this background document.

Where it was possible and helpful to formulate conclusions on the effect or association between coffee consumption and health outcomes, the Committee pooled estimates of the selected studies, using a random effects meta-analysis approach. The estimates of the complementary individual studies were added to the estimates of the individual studies of the existing MA. The Committee combined studies with the following categories of coffee consumption: average consumption of 1-2 cups per day versus less than 1 cup per day, average consumption of 2-4 cups per day versus less than 1 cup per day and high versus low (i.e., the highest intake category compared to the reference group with the lowest intake). The daily average consumption of coffee was based on reported averages or medians in the study reports or, in case this information was not available, on midpoints of reported categories of intake, and/or on 1.2 times the lower bound of an open ended upper intake category.[14] In a few studies, categories of coffee consumption higher than 4 cups/day were evaluated, namely 5 to <7 cups/day and ≥7 cups/day by Mukamal et al. (2009)[15], >4 cups/day by van Dongen et al. (2017)[16] and ≥4 cups/day by Lopez-Garcia et al. (2011)[9]. There were, however, too

few studies available per health outcome to evaluate (and pool estimates of) coffee consumption higher than 4 cups/day.

The Committee did not find SRs of RCTs that addressed the effect of coffee consumption on health outcomes in people with ASCVD. This means that effects of coffee consumption on surrogate outcomes could not be evaluated.

2.5.2 Risk of bias assessment

Ribeiro et al.[8] assessed the risk of bias of the individual studies included in their MA using the Risk Of Bias In Non-randomised Studies – of Interventions (ROBINS-I) tool.[17] The ROBINS-I tool addresses seven domains: confounding, selection of participants into the study, classification of intervention, deviations from intended intervention, missing data, measurement of outcome, and selection of reported results. Each domain was classified as serious, moderate or low risk of bias.

2.5.3 Drawing conclusions

A detailed description of the approach used for drawing conclusions is provided in the background document *Methodology for the evaluation of the evidence.*[6] In short, the Committee drew conclusions on (the certainty of) the evidence regarding associations of coffee consumption with risk of long-term health outcomes in people with (prior) ASCVD, based on the number of studies, number of participants and number of cases that contributed to the evaluation. Also, it took the quality of the studies, in particular the risk of bias, and the heterogeneity between studies into account. The Committee used the decision tree (presented in the background document *Methodology for the evaluation of the evidence*[6]) as a tool to support consistency in drawing conclusions.

3 Associations of coffee consumption

In this chapter the Committee describes the scientific evidence for associations of coffee consumption with long-term health outcomes in people with ASCVD.

Table 1 summarises the characteristics of the prospective cohort studies (including those included in the MA by Ribeiro et al.[8] that provided evidence regarding associations of coffee consumption with all-cause mortality, CVD mortality, total stroke and total MI in people with ASCVD). The Committee pooled the results of the individual prospective cohort studies together with the estimates of the individual studies included in the MA by Ribeiro et al. for these outcomes. The pooled estimates are presented in Table 2. For the other outcomes (for which an insufficient number of studies was found to perform a MA) the estimates per study are presented in Table 3. In Annex B, the characteristics and results of the MA by Ribeiro et al. and the individual prospective cohort studies that were used for the Committee's evaluation are presented in detail.

Table 1 Characteristics of prospective cohort studies contributing to the pooled analyses for the associations of coffee consumption with risk of all-cause mortality, CVD mortality, total stroke and total MI in people with ASCVD: pooled analyses of cohort studies

Aspect	Explanation
Number of studies	All-cause mortality: 6 studies CVD mortality: 4 studies Total stroke: 2 studies Total MI: 3 studies
Number of participants and cases	All-cause mortality: Total number of participants: 21953 Cases: 3406 CVD mortality: Total number of participants: 19123 Cases: 1393 Total CVD: Total number of participants: 11343 Cases: 1191 Total stroke: Total number of participants: 12600 Cases: 304 Total MI: Total number of participants: 14772 Cases: 1686

Study durations	Range from 3.5 to 24 years (NR whether these were the mean/median/maximum follow-up periods)
Dietary exposure	There were estimates reported for 2 (2 studies) 3 (1 study), 4 (4 studies) or 5 (2 studies) categories of coffee consumption
Dietary assessment method	Standardised questionnaire at baseline (2 studies), validated FFQ at baseline (3 studies), validated semi-quantitative FFQ at baseline and every 4 years (1 study), frequency questionnaire at baseline and every year (1 study), dietary questionnaire at baseline and at the 6th, 18th and 42nd month of follow-up (1 study)
Strength of the association	Shown in Table 2 and 3
Study population	People with CVD (1 study), MI (6 studies), stroke (1 study) acute coronary syndrome[a] (1 study); men and women; BMI: 23-28 kg/m^2; medication use: NR for most of the studies; Europe, USA, Asia (Japan), Latin America (Brazil)

Abbreviations: ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; CVD: cardiovascular disease; FFQ: food frequency questionnaire; MI: myocardial infarction; NR: not reported, USA: United States of America.

[a] Acute coronary syndrome included acute myocardial infarction or unstable angina pectoris.

Table 2 Pooled RRs and HRs (95%CI) from prospective cohort studies for the associations of different quantities of coffee consumption compared to ≤1 cup/day and for high versus low intake levels in people with ASCVD, with I^2 indicating the extent of heterogeneity between studies, and *n* indicating the number of studies included

Outcome	RR (95%CI) for 1-2 vs. ≤1 cup/d; I^2; n studies	RR (95%CI) for 2-4 vs. ≤1 cup/d; I^2; n studies	RR (95%CI) for high vs. low[d]; I^2; n studies
All-cause mortality	a. 0.74 (0.46, 1.18); I^2 81%; n=7 b. 0.98 (0.83, 1.14); I^2 24%; n=6 c. 0.72 (0.41, 1.27); I^2 84%; n=6	a. 0.73 (0.47, 1.13); I^2 86%; n=7 b. 0.87 (0.66, 1.14); I^2 71%; n=6	a. 0.99 (0.73, 1.34); I^2 72%; n=7
All-cause mortality, excluding studies without upper limit definition	NA	a. 0.58 (0.31,1.10); I^2 91%; n=4 b. 0.79 (0.56, 1.12); I^2 77%; n=3	NA
CVD mortality	a. 0.81 (0.61, 1.09); I^2 39%; n=5 c. 0.85 (0.64, 1.13); I^2 35%; n=4	a. 0.79 (0.54, 1.15); I^2 72%; n=5 c. 0.70 (0.51, 0.97); I^2 67%; n=4	a. 0.88 (0.58, 1.36); I^2 68%; n=5
CVD mortality, excluding study without upper limit definition	NA	a. 0.73 (0.50, 1.06); I^2 75%; n=3	NA
Total CVD	NA	NA	a. 0.96 (0.86, 1.07); I^2 0%; n=2
Total stroke	NA	NA	a. 0.97 (0.63, 1.49); I^2 0%; n=2

Total MI	NA	NA	a. 0.99 (0.80, 1.22); I^2 29%; n=3

Abbreviations: ASCVD: atherosclerotic cardiovascular disease; CI: confidence interval; CVD: cardiovascular disease; d: day; HR: hazard ratio; MI: myocardial infarction; NA, not applicable; RR: relative risk; vs: versus;.

a = Main result

b = Excluding the study by Miranda et al.[10]

c = excluding the study by Teramoto et al. (subgroup of people with stroke)[11]

[d] High consumption varied between ≥2 and ≥7 cups/day between the studies. Low consumption varied between 0 and ≤2 cups/day between the studies. For the studies without upper limit definition (n=2)[11,18] the assumption was made that the upper bound is estimated as 1.2 times the lower bound of an open-ended upper intake category.

Table 3 HRs or RRs (95%CI) from prospective cohort studies for associations of coffee consumption with health outcomes in people with ASCVD: individual cohort studies[a]

Outcome	Author; N participants; N cases	HR or RR (95%CI) for 1-2 vs. ≤1 cup/d	HR or RR (95%CI) for 2-4 vs. ≤1 cup/d	HR or RR (95%CI) for high vs. low intake[b]
Diabetes	Mozaffarian et al.[12]; 8291; 998	NA	NA	1.19 (0.88, 1.61)
Heart failure	Mukamal et al.[15] 1369; 372	1.01 (0.70, 1.47)	1.04 (0.71, 1.52)	0.71 (0.42, 1.18)
Sudden death	Silletta et al.[19] ; 1369; 264	0.91 (0.65, 1.26)	NA	0.80 (0.55, 1.17)
CHD mortality	van Dongen et al.[16]; 4365; 266	0.73 (0.42, 1.27)	0.77 (0.57, 1.05)	0.68 (0.48, 0.95)
Atrial fibrillation	Mukamal et al.[15]; 1369; 163	0.71 (0.42, 1.20)	0.61 (0.35, 1.04)	0.67 (0.33, 1.34)

Abbreviations: ASCVD: atherosclerotic cardiovascular disease; CHD: coronary heart disease; CI: confidence interval; d: day; HR: hazard ratio; MI: myocardial infarction; N: number; NA: not applicable; NR: not reported; RR: relative risk; vs: versus;.

[a] These studies were not pooled by the Committee since there were too few studies for conclusions with strong evidence.

[b] High consumption varied between ≥2 to >7 cups/day between the studies. Low consumption varied between almost never to <2 cup(s)/d between the studies.

Conclusions:

- **Cohort studies show that people with ASCVD with a consumption of 1-2 cups of coffee per day have likely no different risk of all-cause mortality as compared to those with a coffee consumption of less than 1 cup per day.**
- **There is inconclusive evidence from cohort studies regarding the association between consumption of 2-4 cups of coffee per day compared to less than 1 cup per day and the risk of all-cause mortality in people with ASCVD.**

The following considerations were made by the Committee, following the steps of the decision tree, to come to these conclusions:

1 Number of studies and cases:
There were 6 studies that addressed the association between coffee consumption and all-cause mortality in people with ASCVD.[9-11,15,16,18] One study provided two estimates, one for the subgroup of people with a history of stroke and one for the subgroup of people with a history of MI.[11] In total, there were >500 cases in these studies. This is the first step required to mark the evidence as strong or to conclude that 'an effect is unlikely', for which at least 5 studies and 500 cases are required.

2 Heterogeneity of the study findings:
The pooled estimate of 6 studies (7 estimates) showed no statistically significant association with all-cause mortality when coffee consumption of 1-2 cups per day was compared to less than 1 cup per day, with substantial heterogeneity between studies (I^2 81%). One study showed a strong statistically significant reduced risk of all-cause mortality for higher coffee consumption (Miranda et al.[10]) whereas the other studies did not show an association. In the study by Miranda et al. very few cases contributed to this intake category (n=11), so the Committee cannot exclude the possibility that the finding by Miranda et al. is a chance finding. Moreover, the study by Miranda et al. did not adjust for the use of lipid or blood-pressure lowering medication, energy intake or other dietary factors, which raises concerns about the associations observed being biased by confounding. Because of this, the Committee gave less weight to this study and based its conclusion primarily on the MA in which the study by Miranda et al. was excluded. In that analysis, the I^2 was reduced to 24% and the RR increased to around 1.0 (RR 0.98 (95%CI 0.83, 1.14)). Given that this estimate does not indicate that coffee consumption of 1-2 cups per day compared <1 cup/day is associated with all-cause mortality and that little heterogeneity is present, the Committee concluded that there is likely no association for 1-2 cups of coffee per day.

For 2-4 cups of coffee per day compared to ≤1 cup of coffee per day, no association with mortality risk was observed and heterogeneity was substantial between the 6 studies (7 estimates) contributing to this analysis (I^2 86%). Three studies showed no association and four studies showed a (borderline) statistically significant lower risk of all-cause mortality for higher coffee consumption. No obvious heterogeneity in the direction of the association was observed. A clear explanation for the heterogeneity could not be found by the Committee. Excluding the two studies without an upper limit definition of the intake category (≥2 cups/day)[11,18] did not change the pooled estimate or level of heterogeneity. Also,

the lesser adjustment for potential confounders in the study by Miranda et al.[10] (no adjustment for the use of lipid or blood-pressure lowering medication, energy intake or other dietary factors) is likely no explanation, since excluding this study did not reduce the heterogeneity (I^2 71%) and only marginally changed the pooled estimate. Based on the study by Teramoto et al., it can be suggested that the type of CVD may cause part of the heterogeneity. In their study, participants with MI drinking 2-4 cups of coffee per day had a lower mortality risk, whereas no association was observed in participants with stroke. However, relatively few stroke cases contributed to this analysis (n=20) and the Committee found no other studies in people with stroke that could confirm this hypothesis. Also, regional differences not accounted for in the analyses (e.g., with regard to dietary pattern, lifestyle factors, race) may have contributed to the heterogeneous findings since two of the three studies in this pooled analysis that did not show an association were performed in participants from the USA, whereas those showing an association were performed in participants from Europe, Brazil and Japan. Last, the Committee cannot rule out, but also not confirm, that differences in the definition of the categories of coffee consumption between studies may explain the different results. To conclude, the Committee could not identify one explanation for the heterogeneity between studies. Possibly, multiple factors play a role. Given that this estimate does not indicate that coffee consumption of 2-4 cups per day compared <1 cup/day is associated with all-cause mortality, but that substantial heterogeneity between studies is present for which no explanation was found, the Committee judged (based on the decision tree) the evidence as inconclusive.

The Committee also aimed to evaluate the separate associations of caffeinated versus decaffeinated and filtered versus unfiltered coffee. This is difficult to judge based on the data available since most studies examined caffeinated, filtered coffee. Based on visual expectation of the forest plots, there seem to be no clear indications that (part of) the remaining heterogeneity can be explained by the type of consumed coffee. However, given the limited data on this matter, no firm conclusions can be drawn in this regard.

3 Considerations regarding the quality of the evidence:
Ribeiro et al., who assessed the risk of bias using the ROBINS-I tool, noted as an important limitation that coffee consumption was only assessed at baseline, which is insufficient to retrieve a reliable estimate of coffee consumption over time. This may have led to bias in the classification of the exposure. Another concern relates to potential biased associations due to confounding. Only two studies adjusted for the use of lipid-lowering and blood pressure-lowering medication. Four of the six studies adjusted for intake of dietary factors such as other foods or a dietary score, of which only two included energy intakes. One study concerned an observational

analysis conducted within a RCT. Treatment allocation was included in the multivariable models. No further actions were taken to account for the treatment allocations, such as stratification by treatment allocation.

4 Generalisability:
The studies used for the Committee's evaluation were performed in people with CVD, coronary heart disease (CHD) or stroke. Most of the studies included (mostly) people with CHD, whereas one study included solely stroke survivors (Teramoto et al.[11]). Excluding this study did not result in a different finding and the extent of heterogeneity between studies remained similar. However, subgroup analyses in the study by Teramoto et al. tended to show a different association in participants with stroke as compared to participants with MI, although subgroups were relatively small. Since this observation is based on only one study, the Committee is limited in judging as to whether there are indications to expect that associations differ between people with various types of ASCVD.
Both men and women were included in the studies evaluated by the Committee. However, study results were generally not stratified by sex and therefore it remains unclear whether the associations differ by sex. In contrast to the other studies, the study by Lopez-Garcia et al.[9] included solely women. This study did not show substantially different results from the studies in which both men and women were included. Based on the current evaluation, the Committee sees no reason to expect that associations would be different in men and women.

- **Cohort studies show that people with ASCVD with a consumption of 1-2 cups of coffee per day have likely no different risk of CVD mortality as compared to those with a coffee consumption of less than 1 cup per day.**
- **There is inconclusive evidence from cohort studies regarding the association between consumption of 2-4 cups of coffee per day compared to less than 1 cup per day and the risk of CVD mortality in people with ASCVD.**

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:

1 Number of studies and cases:
There are 5 cohort studies with 19123 participants and 1393 cases that reported on the association between coffee consumption and CVD mortality in people with ASCVD.[9,11,15,16] This is the first step required to mark the evidence as strong or to conclude that 'an effect is unlikely', for which at least 5 studies and 500 cases are required.

2 Heterogeneity of the study findings:

The pooled estimate of 5 studies showed no statistically significant association with CVD mortality when coffee consumption of 1-2 cups/day was compared to less than 1 cup/day, with moderate heterogeneity between studies (I^2 39%). Three studies showed no association and two studies pointed towards a reduced risk of CVD mortality, albeit statistical significance was only reached in one study. There is no obvious heterogeneity in the direction of the association. Most of the studies included (mostly) people with CHD, whereas one study included solely stroke survivors (Teramoto et al.[11]). Excluding this study did not result in a different finding and the extent of heterogeneity between studies remained similar (I^2 35%). Given that this estimate does not indicate that coffee consumption of 1-2 cups/day compared <1 cup/day is associated with CVD mortality and that no substantial heterogeneity is present, the Committee concluded that there is likely no association.

The pooled result for the comparison between 2-4 cups of coffee and ≤1 cup of coffee per day (based on 5 studies) did not substantially differ from the comparison of 1-2 cups of coffee to ≤1 cup of coffee per day. However, substantial heterogeneity between studies in this intake category was observed (I^2 *72*%). There is moderate heterogeneity in direction of the association, which is most likely explained by the study by Teramoto et al., which was performed solely in people with stroke. After the study with stroke survivors, by Teramoto et al., was excluded (as compared to the other studies in people with mostly CHD), a reduced risk of CVD mortality was found (RR 0.70 (0.51, 0.97), but heterogeneity between studies remained high (I^2 67%). This suggest that the type of ASCVD may not entirely explain the heterogeneity. A similar observation was done in the analyses for the association between 1-2 cups of coffee/day and risk of CVD mortality (see above). In the analysis excluding the study by Teramoto et al. (stroke), only one study showed a statistically significant beneficial association, two studies tended to show a beneficial association but were not statistically significant and one study showed no association. There might be multiple factors that explain those differential results, for example differences in reference category used, regional differences, whether medication use, energy intake and/or dietary factors were taken into account in the analyses, or a combination of these factors. However, the Committee could not determine one explaining factor based on the available data. Most likely, multiple factors play a role. Overall, because the main analysis showed no association, the individual studies showed both neutral and beneficial associations, the heterogeneity between studies was substantial and no clear explanation for the heterogeneity could be found, the Committee considered, according to the decision three, the evidence as inconclusive.

The Committee also aimed to evaluate the separate associations of caffeinated versus decaffeinated and filtered versus unfiltered coffee. This is difficult to judge

based on the data available since four studies examined caffeinated, filtered coffee, and from the other study the type of coffee is unknown. Based on visual expectation of the forest plots, it might be suggested that part of the heterogeneity can be explained by the type of coffee consumed. However, given the limited data on this matter, no firm conclusions can be drawn in this regard.

3 Considerations regarding the quality of the evidence:
Ribeiro et al., who assessed the risk of bias using the ROBINS-I tool, noted as an important limitation that coffee consumption was only assessed at baseline, which is insufficient to retrieve a reliable estimate of coffee consumption over time. This may have led to bias in the classification of the exposure. Another concern relates to potential biased results due to confounding. Only one study adjusted for the use of lipid-lowering and blood pressure-lowering medication. All studies adjusted for intake of dietary factors such as other foods or a dietary score, but only two adjusted for energy intake. One study concerned an observational analysis conducted within a RCT. Treatment allocation was included in the multivariable models. No further actions were taken to account for the treatment allocations, such as stratification by treatment allocation.

4 Generalisability:
The studies used for the Committee's evaluation were performed in people with CVD, CHD or stroke. Most of the studies included (mostly) people with CHD, whereas one study included solely stroke survivors (Teramoto et al.[11]). Excluding this study did not result in a different finding and heterogeneity remained similar. However, subgroup analyses in the study by Teramoto et al. tended to show a different association in participants with stroke as compared to participants with MI, although subgroups were relatively small. Since this observation is based on only one study, the Committee is limited in judging as to whether there are indications to expect that associations differ between people with various types of ASCVD.
Both men and women were included in the studies evaluated by the Committee. However, study results were generally not stratified by sex and therefore it remains unclear whether sex influences the study findings. In contrast to the other studies, the study by Lopez-Garcia et al.[9] included solely women. This study did not show substantially different results from the studies in which both men and women were included. Based on the current evaluation, the Committee sees no reason to expect that associations would be different in men and women.

There are too few prospective cohort studies to draw any conclusion on the associations of coffee consumption with risk of total CVD and risk of total stroke in people with ASCVD.

The following considerations were made by the Committee to come to this conclusion, following the steps of the decision tree: There is one MA of two prospective cohort studies per outcome. The pooled results indicate that there is no association between coffee consumption and total CVD risk or total stroke risk, and the two underlying individual studies show no statistically significant findings (not nearly significant either). However, two studies are insufficient to base a conclusion on.

There are too few prospective cohort studies to draw any conclusion on the association between coffee consumption and risk of morbidity or mortality from myocardial infarction in people with ASCVD.

The following considerations were made by the Committee to come to this conclusion, following the steps of the decision tree: There is one MA of three prospective cohort studies included in the evaluation. A total of 14772 participants were included in those studies and 1686 cases of (recurrent) (non-)fatal myocardial infarction were reported.[8] This excludes a conclusion with strong evidence or a conclusion of 'an effect is unlikely', for which at least 5 studies are required. The pooled result indicates that there is no association between coffee consumption and MI risk, and the three underlying individual studies each show no statistically significant findings (not nearly significant either). Three studies are insufficient to draw a conclusion of 'an association is unlikely' and, therefore, the Committee concluded that there is too little research to draw a conclusion.

There are too few prospective cohort studies to draw any conclusion on associations of coffee consumption with risk of diabetes, heart failure, sudden death, CHD mortality or atrial fibrillation in people with ASCVD.

The following considerations were made by the Committee to come to this conclusion, following the steps of the decision tree: There is one individual cohort study per health outcome that addresses these topics. No associations were found for the diabetes, heart failure, sudden death and atrial fibrillation outcomes. The study by van Dongen et al.[16] found a reduced risk of CHD mortality when the highest category of coffee consumption was compared to the lowest category. However, one study provides too little evidence to base conclusions on.

Explanation:
The Committee selected four (from six included in the MA) prospective cohort studies relevant for its evaluation from the MA of Ribeiro et al.[8] More specifically, the studies by Mukamal et al.[18], Mukamal et al.[15], Silletta et al.[19] and van Dongen et al.[16] were selected for the Committee's evaluation. The studies by Fornengo et al.[20] and Notara et al.[21] were not selected for the Committee's evaluation due to the prognostic study

design and/or since the dietary intake likely reflected the pre-event intake. In addition, the Committee selected seven individual prospective cohort studies (Teramoto et al.[11]; Miranda et al.[10]; Lopez-Garcia et al.[9]; Mozaffarian et al.[12], Mukamal et al.[15]; Silletta et al.[19]; van Dongen et al.[16]) in its evaluation of the association between coffee consumption and health outcomes in people with ASCVD. The studies of Mukamal et al., Silletta et al. and van Dongen et al. were also included in the MA of Ribeiro et al. but additionally reported on associations with outcomes that were not addressed in the MA. These were (respectively) heart failure and atrial fibrillation, sudden death, and CHD mortality. Given no other studies reported on these outcomes, no conclusions could be drawn on the associations of coffee consumption with heart failure, sudden death, atrial fibrillation and CHD mortality. Therefore, these three studies are not further explained below. Similarly, the study by Mozaffarian et al. was not further explained below since this was the only study that reported on the diabetes outcome. The MA of Ribeiro et al. and individual studies of Teramoto et al., Miranda et al. and Lopez-Garcia et al. are explained below.

The MA by Ribeiro et al.[8] included 6 prospective cohort studies into the association between coffee consumption and risk of all-cause mortality and cardiovascular outcomes in individuals with a history of myocardial infarction or acute coronary syndrome (of which 4 were relevant for the Committee's evaluation: Mukamal et al. 2004[18], Mukamal et al. 2009[15], Silletta et al.[19] and van Dongen et al.[16]). Per health outcome, 2 to 3 studies were included in the MA. A relatively high compared to low consumption of coffee was associated with reduced CVD mortality risk, without evidence for heterogeneity. This result was based on two studies and was largely driven by the study by van Dongen et al., which contributed 92% weight to the MA. No associations with the risk of all-cause mortality, total CVD, MI or stroke were found. For the all-cause mortality outcome, the level of heterogeneity was substantial. For the all-cause mortality outcome, the authors additionally performed dose-response meta-analyses, and reported there was evidence for a non-linear dose-response relationship (*P*-value for non-linearity 0.001).
For the MI outcome, the dose-response meta-analysis showed a non-significant linear dose-response relation with a RR of 1.01 (95% CI 0.92, 1.11) for each additional cup of coffee. No subgroup or sensitivity analyses were performed in the MA by Ribeiro et al. Coffee consumption was assessed after the index-event, but it cannot be excluded that some studies measured coffee consumption in the acute phase (i.e., within 6 months after disease occurrence) of the index-event. Only two of the included studies used a FFQ to assess coffee consumption (Notara et al. and van Dongen et al.).
The studies included in the MA adjusted for multiple potential confounding variables including age, sex, smoking, alcohol consumption, body mass index (BMI) or obesity, education, physical activity and prevalent diabetes. Two of the studies adjusted the associations for intake of dietary factors such as other foods or a dietary score but not

for energy intake (Silletta et al., Mukamal et al., 2009). In addition, van Dongen et al. adjusted for dietary factors, including energy intake. Only two studies (Mukamal et al., 2004 and Silletta et al.) adjusted for the use of lipid and blood pressure lowering medication.
Ribeiro et al. noted that van Dongen et al. assessed both caffeinated and decaffeinated coffee consumption and found that the RRs in separate categories of caffeinated and decaffeinated coffee consumption were essentially of the same magnitude as compared to the hazard ratios for total coffee consumption.
It should be noted that the studies of Silletta et al., and van Dongen et al. concern observational analyses conducted within RCTs. Both RCTs aimed to investigate the effect of n-3 fatty acid supplementation (plus vitamin E in the study by Silletta et al.). The observational analyses presented here were conducted over all intervention arms and analyses were adjusted for the assigned intervention (interactions with the intervention arms were not tested).
Limitations of this MA are the small number of studies included per health outcome and the heterogeneity of the categories of coffee consumption (in terms of the number of cups of coffee that comprised the categories).
Due to the low number of studies per outcome, Ribeiro et al. reported that a formal assessment of publication bias was not feasible. The funnel plots for the outcomes with 3 or more studies showed there was no clear asymmetry in the estimates.
Ribeiro et al. scored the overall risk of bias using the ROBINS-I tool as serious. Two studies were considered as having moderate risk of bias (Silletta et al. and Fornengo et al.). The most important reason for downgrading the evidence was due to bias in the classification of intervention/exposure, because there was just one baseline assessment of coffee consumption. The studies that measured coffee consumption at least twice overtime were considered at moderate risk of bias.
A GRADE (Grading of Recommendation, Assessment, Development and Evaluation) assessment[22] was performed in the MA by Ribeiro et al.[8] to judge the overall quality of the evidence. Domains in the GRADE assessment include risk of bias, inconsistency, indirectness, imprecision and publication bias. The overall quality (or 'certainty') of the evidence can be graded as very low, low, moderate or high. Ribeiro et al. graded the certainty of the evidence as 'low or very low' (depending on the outcome). This was predominantly due to the serious risk of bias in the studies and due to the confidence interval of the pooled hazard ratio that overlaps 1.0 (except for CVD mortality).
There were no funding sources or authors' conflicts of interest reported in the studies discussed that might interfere with the topic discussed in the current background document.

The study by Teramoto et al.[11] reported no association between coffee consumption and risk of all-cause and CVD mortality in people with a history of stroke. In people with a history of MI, a reduced risk of all-cause mortality was found with higher intakes of

coffee. A similar association was seen with CVD mortality, but not statistically significant. The association between coffee consumption and all-cause mortality was not obviously different between men and women, although the association reached statistical significance in men only. Excluding people who died within the first 5 years of follow-up did not substantially impact the association with all-cause mortality. Such additional analyses were not performed for CVD mortality.
The reason for the lack of association in participants with a history of stroke may have to do with the smaller study population (compared to MI). Moreover, according to the authors a potential explanation might be that chronic caffeinated coffee consumption may increase blood pressure in stroke survivors.
Coffee consumption was measured with an FFQ at baseline. A high correlation was found when the estimated coffee consumption was compared with the consumption measured by the FFQ one year later. The average coffee consumption was not reported. The consumption of no or up to 6 cups of coffee per week was most frequent among the study population.
It is not mentioned by the authors how long after the index-event the data were collected. Given the study is a population-based cohort, the Committee expects it was likely collected outside the acute phase of the index-event (i.e., more than 6 months after diagnosis).
Adjustments for potential confounders were made, including intake of foods but not energy intake. Also, no adjustments for the use of medications were made.
The presence of MI or stroke at baseline of the study was self-reported. No information was given on the use of blood pressure lowering or lipid lowering medication. Given the dates of follow-up of the study (1988-2009), it is likely that such medication use increased during follow-up.
There were no notable funding sources reported and the authors reported to have no conflicts of interest.

The study by Miranda et al.[10] showed that consuming 1-3 cups of coffee per day compared to ≤1 cup/day was associated with a reduced risk of all-cause mortality in Brazilian people with acute coronary syndrome from the ERICO prospective study. Consumption of >3 cups of coffee per day was associated with a higher risk of all-cause mortality. After stratification by smoking status, there was a lower risk of all-cause mortality in never and former smokers, but not in current smokers, who drank 1-2 or 2-3 cups of coffee per day as compared to those drinking ≤1 cup/day. In contrast, an increased mortality risk was observed in former and current smokers, but not in never smokers, drinking >3 cups of coffee/day as compared to those drinking ≤1 cup/day.
People were included when they survived an acute coronary syndrome (MI or unstable angina) event after at least 180 days (so outside the acute phase). Coffee consumption was assessed with a repeated questionnaire based on a validated Brazilian FFQ

(correlation coefficient not reported) and was calculated as the mean across the 5 measurements. Therefore, it is likely to reflect long-term habitual coffee intake. Participants were further asked to specify the type of coffee normally consumed (filter, instant, espresso, mocha pot), and whether this coffee contained caffeine (caffeinated or decaffeinated). The daily coffee consumption (ML/d) related to a reference cup size of 50 mL, which is the household measure adopted in Brazil. The median total coffee intake was 125 mL/day (~2.5 cups/day). The coffee consumption of 2-3 cups/d was most frequent (62%) among the study population and the consumption of ≤1 and >3 cups/day least frequent (8%; 4%). Of the coffee consumers (99% of participants), 98% consumed filtered caffeinated coffee. Deaths were ascertained by death certificates with collaboration of the municipal, the state and the Brazilian Ministry of Health offices. No information was given on the use of medication of study participants. The statistical model was adjusted for multiple factors but not for energy, other food groups or the use of medication.
The Committee notes that the study was rather small in terms of number of included participants and in general relatively few events occurred during the 4-year follow-up. The number of cases contributing to each intake category ranged from 11 death cases in the category of 1-2 cups/day to 48 cases in the category of 2-3 cups/day. This may contribute to unstable effect estimates, especially for the category of 1-2 cups/day with only 11 cases. For stratified analyses according to smoking status, even fewer participants and cases contributed to each intake category.
There were no notable funding sources reported and the authors reported to have no conflicts of interest.

The study by Lopez-Garcia et al.[9] examined the association between filtered caffeinated coffee consumption and risk of all-cause and CVD mortality in 11697 women from the Nurses' Health Study who had experienced a non-fatal CVD event (i.e. MI (11%), stroke (11%), angina pectoris (56%), coronary bypass or percutaneous coronary intervention (21%)). The study showed no association between coffee consumption and risk of all-cause or CVD mortality.
The average coffee consumption in the study population was not reported. The category of <1 cup of coffee a month included most participants (n=4415) and the category of ≥4 cups a day included the fewest (n=595). Repeated validated FFQs were used to assess (filtered) caffeinated coffee consumption. The FFQ was validated against repeated 1-week diet records. A high correlation (r = 0.78) was found for coffee consumption between the two assessment methods. For the data analysis, the cumulative coffee consumption was calculated with all available FFQs from the CVD diagnosis to the end of the follow-up. Therefore, it is likely the coffee consumption reflects the habitual intake outside the acute phase of the index-event. Deaths were reported by next of kin or the postal system or ascertained through the National Death Index. For all deaths, death certificates or medical records were consulted. The

associations of coffee consumption with CVD mortality were adjusted for multiple potential confounders including smoking, blood pressure lowering and lipid lowering medication use, alcohol intake and total energy intake.
A strength of this study is the repeated measurements of coffee consumption (after the first CVD event) to estimate habitual coffee consumption and to account for changes over the follow-up period. In addition, the type of coffee consumed (caffeinated, filtered in particular) was reported. Other strengths include the large number of participants, the large number of events, the long follow-up and the updated information on potential confounders that was taken into account in the data analyses. In particular, regarding the use of medication, the authors note that medical treatment of CVD has changed over time. Strong clinical evidence on beneficial effects of ACE-inhibitors and statins date from (respectively) 1991 and 1994, and the current standard CVD treatments were set long after the start of the study. The data-analyses adjusted for the use of medication, which was updated repeatedly during the follow-up of the study.
Sensitivity analyses where potential confounding due to changes in coffee consumption ware accounted for, or where coffee consumption was associated with shorter-term risk of CVD mortality (two years), showed results similar to those from the main analyses.
There were no notable funding sources reported and the authors reported to have no conflicts of interest.

4 Summary of conclusions

The Committee's conclusions regarding associations of coffee consumption with health outcomes in people with ASCVD are summarised in Table 4.

Table 4 Overview of conclusions regarding the associations of coffee consumption with health outcomes in people with ASCVD, based on prospective cohort studies

Health outcome	Conclusion
All-cause mortality	1-2 vs. ≤1 cups of coffee/d: likely no association 2-4 vs. ≤1 cups of coffee/d: inconclusive evidence
CVD mortality	1-2 vs. ≤1 cups of coffee/d: likely no association 2-4 vs. ≤1 cups of coffee/d: inconclusive evidence
Total CVD	Too little research
Morbidity or mortality due to stroke	Too little research
Morbidity or mortality due to myocardial infarction	Too little research
Diabetes	Too little research
Heart failure	Too little research
Sudden death	Too little research
CHD mortality	Too little research
Atrial fibrillation	Too little research

Abbreviations: ASCVD: atherosclerotic cardiovascular disease; CHD: coronary heart disease; CVD: cardiovascular disease.

Observations regarding the type of coffee consumed

The Committee aimed to examine the relationship of caffeinated coffee and decaffeinated coffee, and of filtered coffee and unfiltered coffee separately, since it is presumed that associations of coffee consumption with health outcomes may depend on whether or not the coffee is caffeinated and whether or not it is filtered. Moreover, the guideline for coffee consumption in the Dutch dietary guidelines 2015 is: 'Replace unfiltered coffee by filtered coffee'.[3] The available data were, however, not appropriate to address this question. Most studies examined consumption of filtered, caffeinated coffee. From two studies it is unclear if it concerned filtered or unfiltered coffee (or both) and from two studies it is unclear if it concerned caffeinated or decaffeinated coffee (or both). Therefore, it was not possible to examine whether the relationship of coffee with health outcomes depends on the type of coffee consumed. Since the majority of studies addressed filtered, caffeinated coffee, the conclusions drawn by the Committee predominantly apply to filtered and caffeinated coffee. Whether unfiltered coffee has a different (unfavourable) relationship with health outcomes in people with ASCVD than filtered coffee remains uncertain based on the evaluated studies.

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Annexes

Annex A Search strategy and study selection

A.1 Search strategy systematic reviews and meta-analyses

The Committee performed a literature search to identify relevant systematic reviews (SRs) including meta-analyses (MAs) on the relationship between coffee consumption and health outcomes in people with atherosclerotic cardiovascular disease. PubMed and Scopus were searched for literature on 11th May 2021 using the following search strategies:

PubMed

(Coronary disease [MeSH] OR Acute coronary syndrome [MeSH] OR Angina pectoris [MeSH] OR Coronary artery disease [MeSH] OR Myocardial infarction [MeSH] OR Peripheral arterial disease [MeSH] OR Intermittent claudication [MeSH] OR Stroke [MeSH] OR Brain ischemia [MeSH] OR Cerebrovascular disorders [MeSH] OR Percutaneous coronary intervention [MeSH] OR Coronary artery bypass [MeSH] OR Coronary disease [TIAB] OR Coronary heart disease [TIAB] OR Acute coronary syndrome [TIAB] OR Angina pectoris [TIAB] OR Angina [TIAB] OR Ischemic heart disease [TIAB] OR Ischaemic heart disease [TIAB] OR Coronary artery disease [TIAB] OR Coronary Arteriosclerosis [TIAB] OR Myocardial infarction [TIAB] OR Heart attack [TIAB] OR Peripheral arterial disease [TIAB] OR Peripheral vascular disease [TIAB] OR Intermittent claudication [TIAB] OR Stroke [TIAB] OR Acute stroke [TIAB] OR Cerebrovascular Apoplexy [TIAB] OR Apoplexy [TIAB] OR Ischemic stroke [TIAB] OR Ischaemic stroke [TIAB] OR Hemorrhagic stroke [TIAB] OR Haemorrhagic stroke [TIAB] OR Cerebrovascular accident [TIAB] OR Acute cerebrovascular accident [TIAB] OR Cerebrovascular stroke [TIAB] OR Brain vascular accident [TIAB] OR Brain ischemia [TIAB] OR Cerebral ischemia [TIAB] OR Cerebral stroke [TIAB] OR Brain accident [TIAB] OR Brain infarction [TIAB] OR Cerebral infarction [TIAB] OR Transient ischemic attack [TIAB] OR TIA [TIAB] OR Cerebrovascular* [TIAB] OR Subarachnoid haemorrhage [TIAB] OR Intracerebral hemorrhage [TIAB] OR Intracranial hemorrhages [TIAB] OR Coronary revascularization [TIAB] OR Percutaneous coronary intervention [TIAB] OR Coronary artery bypass graft surgery [TIAB] OR Percutaneous transluminal coronary angioplasty [TIAB] OR Percutaneous transluminal angioplasty [TIAB] OR Coronary angioplasty [TIAB] OR Atherosclerotic cardiovascular disease [TIAB] OR Carotid artery disease [TIAB] OR CHD [TIAB] OR ACS [TIAB] OR IHD [TIAB] OR CAD [TIAB] OR MI [TIAB] OR AMI [TIAB] OR PAD [TIAB] OR CVA [TIAB] OR CVAs [TIAB] OR TIA [TIAB] OR PCI [TIAB] OR CABG [TIAB] OR PTCA [TIAB] OR PTA [TIAB] OR ASCVD [TIAB])

AND

(coffee[MeSH Terms] OR coffee[tiab] OR decaffeinated[tiab] OR espresso[tiab] OR "Caffeine"[Mesh] OR caffeine[tiab])

AND

(Systematic review[publication type] OR Meta-analysis[publication type] OR review[tiab] OR "meta-analysis"[tiab] OR meta analysis [tiab] OR metaanalysis[tiab] OR quantitative review[tiab] OR quantitative overview[tiab] OR systematic review[tiab] OR systematic overview[tiab] OR methodologic review[tiab] OR methodologic overview[tiab])

Limit: from 2000

Scopus

(TITLE-ABS("Coronary disease") OR TITLE-ABS("Acute coronary syndrome") OR TITLE-ABS("Angina pectoris") OR TITLE-ABS("Coronary artery disease") OR TITLE-ABS("Myocardial infarction") OR TITLE-ABS("Peripheral arterial disease") OR TITLE-ABS("Intermittent claudication") OR TITLE-ABS(Stroke) OR TITLE-ABS("Brain ischemia") OR TITLE-ABS("Cerebrovascular disorders") OR TITLE-ABS("Percutaneous coronary intervention") OR TITLE-ABS("Coronary artery bypass") OR TITLE-ABS("Coronary heart disease") OR TITLE-ABS(Angina) OR TITLE-ABS("Ischemic heart disease") OR TITLE-ABS("Ischaemic heart disease") OR TITLE-ABS("Coronary Arteriosclerosis") OR TITLE-ABS("Heart attack") OR TITLE-ABS("Peripheral vascular disease") OR TITLE-ABS("Acute stroke") OR TITLE-ABS("Cerebrovascular Apoplexy") OR TITLE-ABS(Apoplexy) OR TITLE-ABS("Ischemic stroke") OR TITLE-ABS("Ischaemic stroke") OR TITLE-ABS("Hemorrhagic stroke") OR TITLE-ABS("Haemorrhagic stroke") OR TITLE-ABS("Cerebrovascular accident") OR TITLE-ABS("Acute cerebrovascular accident") OR TITLE-ABS("Cerebrovascular stroke") OR TITLE-ABS("Brain vascular accident") OR TITLE-ABS("Brain ischemia") OR TITLE-ABS("Cerebral ischemia") OR TITLE-ABS("Cerebral stroke") OR TITLE-ABS("Brain accident") OR TITLE-ABS("Brain infarction") OR TITLE-ABS("Cerebral infarction") OR TITLE-ABS("Transient ischemic attack") OR TITLE-ABS(TIA) OR TITLE-ABS(Cerebrovascular*) OR TITLE-ABS("Subarachnoid haemorrhage") OR TITLE-ABS("Intracerebral hemorrhage") OR TITLE-ABS("Intracranial hemorrhages") OR TITLE-ABS("Coronary revascularization") OR TITLE-ABS("Percutaneous coronary intervention") OR TITLE-ABS("Coronary artery bypass graft surgery") OR TITLE-ABS("Percutaneous transluminal coronary angioplasty") OR TITLE-ABS("Percutaneous transluminal angioplasty") OR TITLE-ABS("Coronary angioplasty") OR TITLE-ABS("Atherosclerotic cardiovascular disease") OR TITLE-ABS("Carotid artery disease") OR TITLE-ABS(CHD) OR TITLE-ABS(ACS) OR TITLE-ABS(IHD) OR TITLE-ABS(CAD) OR TITLE-ABS(MI) OR TITLE-ABS(AMI)

OR TITLE-ABS(PAD) OR TITLE-ABS(CVA) OR TITLE-ABS(CVAs) OR TITLE-ABS(TIA) OR TITLE-ABS(PCI) OR TITLE-ABS(CABG) OR TITLE-ABS(PTCA) OR TITLE-ABS(PTA) OR TITLE-ABS(ASCVD))

AND

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AND

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Limit: from 2000

A.2 Search strategy RCTs

The Committee performed a literature search to identify relevant individual randomised controlled trials that were not included in an MA. PubMed and Scopus were searched for literature on 24th August 2022 using the following search strategies:

Pubmed

(“Coronary disease” [MeSH] OR “Acute coronary syndrome” [MeSH] OR “Angina pectoris” [MeSH] OR “Coronary artery disease” [MeSH] OR “Myocardial infarction” [MeSH] OR “Peripheral arterial disease” [MeSH] OR “Intermittent claudication” [MeSH] OR “Stroke” [MeSH] OR “Brain ischemia” [MeSH] OR “Cerebrovascular disorders” [MeSH] OR “Percutaneous coronary intervention” [MeSH] OR “Coronary artery bypass” [MeSH] OR “Coronary disease” [TIAB] OR “Coronary heart disease” [TIAB] OR “Acute coronary syndrome” [TIAB] OR “Angina pectoris” [TIAB] OR “Angina” [TIAB] OR “Ischemic heart disease” [TIAB] OR Ischaemic heart disease [TIAB] OR Coronary artery disease [TIAB] OR “Coronary Arteriosclerosis” [TIAB] OR “Myocardial infarction” [TIAB] OR “Heart attack” [TIAB] OR “Peripheral arterial disease” [TIAB] OR “Peripheral vascular disease” [TIAB] OR “Intermittent claudication” [TIAB] OR “Stroke” [TIAB] OR “Acute stroke” [TIAB] OR “Cerebrovascular Apoplexy” [TIAB] OR “Apoplexy” [TIAB] OR “Ischemic stroke” [TIAB] OR “Ischaemic stroke” [TIAB] OR “Hemorrhagic stroke” [TIAB] OR “Haemorrhagic stroke” [TIAB] OR “Cerebrovascular accident” [TIAB] OR “Acute cerebrovascular accident” [TIAB] OR “Cerebrovascular stroke” [TIAB] OR “Brain vascular accident” [TIAB] OR “Brain ischemia” [TIAB] OR “Cerebral ischemia” [TIAB]

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AND

(“coffee”[MeSH Terms] OR “coffee”[tiab] OR “decaffeinated”[tiab] OR “espresso”[tiab] OR "Caffeine"[Mesh] OR “caffeine”[tiab])

AND

("Clinical Trials as Topic"[Mesh] OR "Clinical Trial" [publication type] OR "Cross-Over Studies"[Mesh] OR "Double-Blind Method"[Mesh] OR "Single-Blind Method"[Mesh] OR "Controlled Before-After Studies"[Mesh] OR "Historically Controlled Study"[Mesh] OR randomized[tiab] OR randomised[tiab] OR RCT[tiab] OR controlled*[tiab] OR placebo[tiab] OR clinical trial[tiab] OR trial[tiab] OR intervention[tiab])

Limit: from 2000

Scopus

TITLE-ABS("Coronary disease") OR TITLE-ABS("Acute coronary syndrome") OR TITLE-ABS("Angina pectoris") OR TITLE-ABS("Coronary artery disease") OR TITLE-ABS("Myocardial infarction") OR TITLE-ABS("Peripheral arterial disease") OR TITLE-ABS("Intermittent claudication") OR TITLE-ABS(Stroke) OR TITLE-ABS("Brain ischemia") OR TITLE-ABS("Cerebrovascular disorders") OR TITLE-ABS("Percutaneous coronary intervention") OR TITLE-ABS("Coronary artery bypass") OR TITLE-ABS("Coronary heart disease") OR TITLE-ABS(Angina) OR TITLE-ABS("Ischemic heart disease") OR TITLE-ABS("Ischaemic heart disease") OR TITLE-ABS("Coronary Arteriosclerosis") OR TITLE-ABS("Heart attack") OR TITLE-ABS("Peripheral vascular disease") OR TITLE-ABS("Acute stroke") OR TITLE-ABS("Cerebrovascular Apoplexy") OR TITLE-ABS(Apoplexy) OR TITLE-ABS("Ischemic stroke") OR TITLE-ABS("Ischaemic stroke") OR TITLE-

ABS("Hemorrhagic stroke") OR TITLE-ABS("Haemorrhagic stroke") OR TITLE-ABS("Cerebrovascular accident") OR TITLE-ABS("Acute cerebrovascular accident") OR TITLE-ABS("Cerebrovascular stroke") OR TITLE-ABS("Brain vascular accident") OR TITLE-ABS("Brain ischemia") OR TITLE-ABS("Cerebral ischemia") OR TITLE-ABS("Cerebral stroke") OR TITLE-ABS("Brain accident") OR TITLE-ABS("Brain infarction") OR TITLE-ABS("Cerebral infarction") OR TITLE-ABS("Transient ischemic attack") OR TITLE-ABS(TIA) OR TITLE-ABS(Cerebrovascular*) OR TITLE-ABS("Subarachnoid haemorrhage") OR TITLE-ABS("Intracerebral hemorrhage") OR TITLE-ABS("Intracranial hemorrhages") OR TITLE-ABS("Coronary revascularization") OR TITLE-ABS("Percutaneous coronary intervention") OR TITLE-ABS("Coronary artery bypass graft surgery") OR TITLE-ABS("Percutaneous transluminal coronary angioplasty") OR TITLE-ABS("Percutaneous transluminal angioplasty") OR TITLE-ABS("Coronary angioplasty") OR TITLE-ABS("Atherosclerotic cardiovascular disease") OR TITLE-ABS("Carotid artery disease") OR TITLE-ABS(CHD) OR TITLE-ABS(ACS) OR TITLE-ABS(IHD) OR TITLE-ABS(CAD) OR TITLE-ABS(MI) OR TITLE-ABS(AMI) OR TITLE-ABS(PAD) OR TITLE-ABS(CVA) OR TITLE-ABS(CVAs) OR TITLE-ABS(TIA) OR TITLE-ABS(PCI) OR TITLE-ABS(CABG) OR TITLE-ABS(PTCA) OR TITLE-ABS(PTA) OR TITLE-ABS(ASCVD)

AND

TITLE-ABS(“coffee”) OR TITLE-ABS(“decaffeinated”) OR TITLE-ABS(“espresso”) OR TITLE-ABS(“caffeine”)

AND

TITLE-ABS-KEY ("Clinical Trial") OR TITLE-ABS-KEY ("Cross-Over Studies”) OR TITLE-ABS-KEY("Double-Blind Method") OR TITLE-ABS-KEY("Single-Blind Method") OR TITLE-ABS-KEY("Controlled Before-After Studies") OR TITLE-ABS-KEY("Historically Controlled Study") OR TITLE-ABS-KEY(randomized) OR TITLE-ABS-KEY(randomised) OR TITLE-ABS-KEY(RCT) OR TITLE-ABS-KEY(controlled*) OR TITLE-ABS-KEY(placebo) OR TITLE-ABS-KEY(“clinical trial”) OR TITLE-ABS-KEY(trial) OR TITLE-ABS-KEY(intervention)

Limit from: 2000

A.3 Selection of SRs and MAs

Step 1. Identification
216 records retrieved:

- PubMed: 98

- Scopus: 118

75 duplicates excluded

Step 2. Screening
141 records screened,
99 records excluded after first selection

Step 3. Eligibility
42 full-texts assessed,
40 records excluded after second selection due to:

- No systematic review
- Different study population
- No outcome of interest
- No full text available
- Other language

Step 4. Inclusion
2 records included

A.4 Selection of RCTs

Step 1. Identification
533 records retrieved:

- PubMed: 162
- Scopus: 371

108 duplicates excluded

Step 2. Screening
425 records screened,
416 records excluded after first selection

Step 3. Eligibility
9 full-texts assessed,
8 records excluded after second selection due to:

- Different study population
- Different study design
- No exposure of interest
- Cohort study already included

Step 4. Inclusion
1 record included

Annex B Summary of studies included in the Committee's evaluation

Supplementary Table B1 Summary of associations of coffee consumption with risk of health outcomes in people with ASCVD: meta-analysis of prospective cohort studies of Ribeiro et al.

Aspect	Ribeiro et al. 2020[8]
Study durations	3.5 to 10 years
Number of studies; number of participants; number of cases per health outcome	All-cause mortality: 3 studies; 7636 participants; 1549 cases Total CVD: 2 studies; 11343 participants; 1191 cases CVD mortality: 2 studies; 5734 participants; 556 cases Myocardial infarction[a]: 3 studies; 14772 participants; 1686 cases Stroke[a]: 2 studies; 12600 participants; 304 cases
Dietary exposure (number of studies)	Caffeinated coffee consumption (2 studies) or total coffee consumption (4 studies) Lowest category of coffee consumption was defined in the included studies as 0 cups/day or (almost) never, and the highest category was defined as ≥2 cups/day, ≥3 cups/day or ≥7 cups/day
Dietary assessment method (number of studies)	Standardised questionnaire at baseline (2 studies) and at end of follow-up (1 study), validated FFQ at baseline (2 studies), dietary questionnaire at baseline and at the 6th, 18th and 42nd month of follow-up (1 study)
Heterogeneity (I^2)	All-cause mortality: Yes (58%) Total CVD: No (0%) CVD mortality: No (0%) Myocardial infarction: No (29%) Stroke: No (0%)
Strength of the association: RR (95% CI)[b]	Highest versus lowest category of coffee consumption: ALL-CAUSE MORTALITY: 0.85 (0.63, 1.13) TOTAL CVD: 0.96 (0.86, 1.07) CVD MORTALITY: 0.70 (0.54, 0.91) MYOCARDIAL INFARCTION: 0.99 (0.80, 1.22) STROKE: 0.97 (0.63, 1.49)
Study population	People with myocardial infarction or acute coronary syndrome[c]; men and women; BMI: NR; Medication use: NR; Europe, USA

Abbreviations: BMI: body mass index; CI: confidence interval, CVD: cardiovascular disease; FFQ: food frequency questionnaire; NR: not reported, RR: relative risk; USA: United States of America.

[a] Includes both fatal and non-fatal cases.

[b] Result from a random-effects model. All studies included in the meta-analysis adjusted the associations for major potential confounders, including age, smoking, alcohol consumption, body mass index, socioeconomic status and education, physical activity and history of diabetes and hypertension.

[c] Acute coronary syndrome included acute myocardial infarction or unstable angina pectoris.

Supplementary Table B2 Summary of associations of coffee consumption with risk of health outcomes in people with atherosclerotic cardiovascular disease: prospective cohort studies of Teramoto et al. and Miranda et al.

Aspect	Teramoto et al., 2021[11]	Miranda et al., 2021[10]
Study duration	Median 18.5 years (1988-2009)	Mean 4.1 years (2009-2013)
Primary event	CHD or stroke	CHD

Cohort name	Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC study)	ERICO cohort
Number of participants; number of cases	In 478 stroke survivors: 232 cases of all-cause mortality, 107 cases of CVD mortality In 1214 MI survivors: 355 cases of all-cause mortality; 151 cases of CVD mortality	928 participants; 111 cases of all-cause mortality
Dietary exposure	Total coffee The type of coffee, such as decaffeinated or caffeinated, was not asked because decaffeinated coffee was not common, and most participants consumed instant or drip brewed coffee during the baseline survey period in Japan.	Total coffee consumption Coffee was mainly filtered and caffeinated (98% of study participants)
Dietary assessment method	Validated FFQ; correlation coefficient from validation study for coffee consumption was 0.86.	Frequency questionnaire based on a validated Brazilian FFQ (correlation coefficient NR) assessed at baseline and every year of follow-up
Strength of the association: HR (95% CI)[a]	Compared to none • In stroke survivors: ALL-CAUSE MORTALITY 1 to 6 cups/wk: 1.31 (0.94, 1.82) 1 cup/d: 0.81 (0.44, 1.50) ≥2 cups/d: 1.52 (0.87, 2.68) *P for linear trend = 0.32* CVD MORTALITY 1 to 6 cups/wk: 1.36 (0.84, 2.21) 1 cup/d: 0.36 (0.10, 1.23) ≥2 cups/d: 2.03 (0.90, 4.59) *P for linear trend = 0.40* • In MI survivors: ALL-CAUSE MORTALITY 1 to 6 cups/wk: 0.69 (0.53, 0.91) 1 cup/d: 0.78 (0.55, 1.10) ≥2 cups/d: 0.61 (0.41, 0.90) *P for linear trend = 0.03* CVD MORTALITY 1 to 6 cups/wk: 0.84 (0.55, 1.28) 1 cup/d: 0.81 (0.47, 1.40)	Compared to ≤1 cup/d 1 to 2 cups/d: 0.13 (0.06, 0.29) 2-3 cups/d: 0.22 (0.13, 0.39) >3 cups/d: 2.12 (1.06, 4.24)

	≥2 cups/d: 0.58 (0.31, 1.09) *P for linear trend = 0.10*	
Study population	People with a history of MI or stroke; BMI[b]: 23 (SD unknown) kg/m^2; men (37 to 71% over the categories of coffee consumption) and women; medication: NR; Japan	People with a prior acute myocardial infarction or unstable angina; BMI[b]: 27 kg/m^2 (SD unknown); men (60%) and women (40%); medication: NR; South America (Brazil)

Abbreviations: Abbreviations: BMI: body mass index, CHD: coronary heart disease, CI: confidence interval, CVD: cardiovascular disease, d: day; FFQ: food frequency questionnaire, HR: hazard ratio, MI: myocardial infarction, NR: not reported, RR: relative risk, SD: standard deviation; wk: week.
Footnotes:
[a] The following adjustments for confounders were applied: Teramoto et al.: age, sex, history of hypertension, history of diabetes, body mass index, smoking status, alcohol consumption, hours of exercise, hours of walking, perceived mental stress, educational level, regular employment, dietary intakes of vegetable, fish, fruits, soybeans; Miranda et al.: age, sex, race/skin colour, educational attainment, marital status, BMI, physical activity, smoking status, hypertension, diabetes, dyslipidaemia, ACS subtype.
[b] Mean ± standard deviation.

Supplementary Table B3 Summary of associations of coffee consumption with risk of health outcomes in people with atherosclerotic cardiovascular disease: prospective cohort studies of Lopez-Garcia et al. and Mozaffarian et al.

Aspect	Lopez-Garcia et al., 2011[9];	Mozaffarian et al., 2007[12]
Study duration	Maximum 24 years (1980-2004)	Mean 3.2 years
Primary event	CVD	CHD
Cohort name	Nurses' Health Study (NHS)	GISSI-Prevenzione study
Number of participants; number of cases	11697 participants; 1159 cases of all-cause mortality 579 cases of CVD mortality	8291 participants; 998 cases of diabetes
Dietary exposure	Filtered caffeinated coffee consumption	Total coffee consumption (the types of coffee mostly consumed are espresso and mocha, thus the coffee is partially filtered)
Dietary assessment method	Validated semi-quantitative FFQs administered in 1980, 1984, 1986, 1990, 1994, 1998 and 2002 (cumulative average used for analysis).	Questionnaire into the usual consumption of several food items at baseline and at the 6th and 18th month of follow-up.
Strength of the association: HR or RR (95% CI)[a]	Compared to <1 cup/mo ALL-CAUSE MORTALITY: 1 cup/mo to 4 cups/wk: 1.04 (0.86, 1.27) 5-7 cups/wk: 1.13 (0.95, 1.36) 2-3 cups/d: 1.01 (0.95, 1.36) ≥4 cups/d: 1.18 (0.89, 1.56) *P for linear trend = 0.91*	Compared to never or rarely DIABETES: ≥5 cups/d: 1.19 (0.88, 1.61)

	CVD MORTALITY: up to 4 cups/wk: 0.99 (0.75, 1.31) 5-7 cups/wk: 1.03 (0.80, 1.35) 2-3 cups/d: 0.97 (0.78, 1.21) ≥4 cups/d: 1.25 (0.85, 1.84) *P for linear trend=0.76*	
Study population	People with prior MI, stroke, angina pectoris, coronary bypass or coronary angioplasty[c]; BMI[b]: 27 ± 6 kg/m^2; women (100%); % medication use over the categories of coffee consumption ranged from: statins 26 to 36%, diuretics 15 to 20%, β blockers 24 to 34%, calcium channel blockers 23 to 25%, ACE inhibitors 12 to 17%, other blood pressure lowering medication 9 to 13%; USA	People with recent (≤3 months) myocardial infarction; Average BMI[b]: 26.3 ± 3.4; men (87%) and women; mediation: ACE inhibitors: 45%, Beta-blockers: 47%, diuretics: 8%, cholesterol-lowering medication: increased from 5% at start of the study to 45% at 3.5 years.

Abbreviations: Abbreviations: ACE: angiotensin-converting enzyme, BMI: body mass index, CHD: coronary heart disease, CI: confidence interval, CVD: cardiovascular disease, d: day, FFQ: food frequency questionnaire, GISSI-Prevenzione trial: Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocárdico-Prevenzione trial, HR: hazard ratio, MI: myocardial infarction, mo: month, RR: relative risk, USA: United States of America; wk: week.

[a] The following adjustments for confounders were applied: Lopez-Garcia et al.: age, smoking status, BMI, physical activity, parental history of MI, menopausal status and use of hormonal replacement therapy, hypertension, hypercholesterolemia, type 2 diabetes, medication use (aspirin, diuretics, β blockers, calcium channel blockers, ACE inhibitors, other blood pressure medications, statins, other cholesterol-lowering drugs), dietary factors (daily multivitamin and vitamin E supplement use, total energy intake, glycaemic load, folate intake, quintiles of polyunsaturated, saturated, total n-3, and trans-fat intakes); Mozaffarian et al.: age, sex, BMI, physician-diagnosed hypertension, previous acute myocardial infarction, current smoking, former smoking, days from acute myocardial infarction to enrolment, NYHA class, angina, positive exercise stress test, exercise capacity, inability to undergo exercise testing, fish oil supplements, vitamin E supplements, ACE inhibitor, beta-blocker, diuretic, lipid-lowering medication, Mediterranean diet score, wine consumption, cheese consumption.

[b] Mean ± standard deviation.

[c] Of the total of 11,697 women who had experience a nonfatal CVD event (and were included in the current analysis), 11.1% had a MI, 11.3% a stroke, 56.1% angina pectoris, and 21.4% a coronary bypass or coronary angioplasty.

Supplementary Table B4 Summary of associations of coffee consumption with risk of health outcomes in people with atherosclerotic cardiovascular disease: prospective cohort studies of Mukamal et al. and Silletta et al.

Aspect	Mukamal et al. 2009[15]	Silletta et al. 2007[19]
Study duration	7-10 years (mean/median NR)	Maximum 3.5 years
Primary event	CHD	CHD
Cohort name	Stockholm Heart Epidemiology Program (SHEEP)	GISSI-Prevenzione study

Number of participants; number of cases	1369 participants; 372 cases of heart failure 163 cases of atrial fibrillation	11231 participants; 264 cases of sudden death
Dietary exposure	Filtered caffeinated coffee consumption	Total coffee consumption
Dietary assessment method	Standardised questionnaire at baseline	Dietary questionnaire at baseline and at the 6th, 18th and 42nd month of follow-up
Strength of the association: HR or RR (95% CI)[a]	Compared to <1 cup/d HEART FAILURE: 1 to <3 cups/d: 1.01 (0.70, 1.47) 3 to <5 cups/d: 1.04 (0.71, 1.52) 5 to <7 cups/d: 0.91 (0.60, 1.38) ≥7 cups/d: 0.71 (0.42, 1.18) *P for linear trend=0.11* ATRIAL FIBRILATION: 1 to <3 cups/d: 0.71 (0.42, 1.20) 3 to <5 cups/d: 0.61 (0.35, 1.04) 5 to <7 cups/d: 0.61 (0.34, 1.10) ≥7 cups/d: 0.67 (0.33, 1.34) *P for linear trend=0.32*	Compared to (almost) never SUDDEN DEATH: <2 cups/d: 0.91 (0.65, 1.26) ≥2 to 4 cups/d: 0.80 (0.55, 1.17) *P for linear trend=0.24*
Study population	People with acute MI; BMI >30 kg/m^2: ~17%; men (58 to 83% per category of coffee consumption) and women; % medication use over the categories of coffee consumption ranged from: β blockers 73 to 80%, calcium antagonists 5 to 14%, diuretics 20 to 31%, ACE inhibitors 6 to 16%; Europe	People with (prior) MI; BMI[b]: 26.5 ± 3.5 kg/m^2; men (85%) and women; % medication use over the categories of coffee consumption ranged from: ACE inhibitors 43 to 49%, β blockers 40 to 51%; lipid lowering medication use increased from 5% at baseline to 50% after 3.5 years follow-up; Europe

Abbreviations: Abbreviations: ACE: angiotensin-converting enzyme, BMI: body mass index, CHD: coronary heart disease, CI: confidence interval, d: day, GISSI-Prevenzione trial: Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocárdico-Prevenzione trial, HR: hazard ratio, MI: myocardial infarction, NR: not reported, RR: relative risk.

[a] The following adjustments for confounders were applied: Mukamal et al.: age, sex, diabetes, smoking, obesity, physical inactivity, alcohol consumption, tea consumption, education; Silletta et al.: age, gender, smoking, time from MI to enrolment, prior MI previous to index MI, BMI, history of hypertension, history of diabetes mellitus, peripheral vascular disease, electrical instability, results of exercise stress testing, left ventricular ejection fraction, New York Heart Association class, Canadian Cardiovascular Society angina symptoms, revascularization procedures, n-3 PUFA use, vitamin E use, antiplatelet use, ACE inhibitor use, lipid-lowering medication use, β-blocker use, intake of cooked vegetables, raw vegetables, fruit, fish, olive oil, other oil, butter, cheese, wine.

[b] Mean ± standard deviation.

Supplementary Table B5 Summary of associations of coffee consumption with risk of health outcomes in people with atherosclerotic cardiovascular disease: prospective cohort study of van Dongen et al.

Aspect	van Dongen et al. 2017[16]
Study duration	Maximum 12 years (2002-2013); median 7.1 years
Primary event	CHD
Cohort name	Alpha Omega Cohort
Number of participants; number of cases	4837; 266 cases of CHD mortality
Dietary exposure	Total coffee consumption (caffeinated and decaffeinated)
Dietary assessment method	Validated FFQ (correlation coefficient NR)
Strength of the association: HR (95% CI)[a]	Compared to 0-2 cups/d CHD MORTALITY: >2-4 cups/d: 0.77 (0.57, 1.05) >4 cups/d: 0.68 (0.48, 0.95) *P for linear trend=0.04*
Study population	People with (prior) MI; BMI[b]: 28 ± 4 kg/m^2: men (79%) and women (21%); medication: antihypertensive drugs (90%), lipid-modifying drugs (87%); Europe

Abbreviations: Abbreviations: BMI: body mass index, CHD: coronary heart disease, CI: confidence interval, d: day, FFQ: food frequency questionnaire, HR: hazard ratio, MI: myocardial infarction, RR: relative risk.

[a] The following adjustments for confounders were applied: age, sex, treatment code, prevalent diabetes, BMI, physical activity, educational level, smoking status, alcohol use, total energy, black or green tea, whole grains, red or processed meats, dairy, vegetables or fruits, chocolate, sugar-sweetened beverages, plant oils, legumes, nuts or seeds.

[b] Mean ± standard deviation.

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The Health Council receives most requests for advice from the Ministers of Health, Welfare and Sport, Infrastructure and Water Management, Social Affairs and Employment, and Agriculture, Nature and Food Quality. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.
Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity. The reports are available to the public.

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