Coffee

No. 2021/41He, The Hague, November 16, 2021

Background document to:
Dutch dietary guidelines for people with type 2 diabetes
No. 2021/41e, The Hague, November 16, 2021

Health Council of the Netherlands

contents

01 introduction

The current background document belongs to the advisory report *Dutch dietary guidelines for people with type 2 diabetes*.[1] It describes the methodology for the search, selection and evaluation of the literature regarding the relationship of coffee consumption with health outcomes in people with type 2 diabetes. The current background document furthermore describes the scientific evidence on this topic and the conclusions that have been drawn by the Health Council's Committee on Nutrition.

1.1 Definition of coffee

Coffee is a drink made of milled coffee beans, which naturally contain 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 particularly 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, 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, where 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*[3], which is as follows:
Replace unfiltered coffee by filtered coffee.

This guideline is applicable to the general Dutch adult population. The Council has not previously made specific dietary recommendations for people with type 2 diabetes.

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

02 methodology

2.1 Research question

The Committee aimed to answer the following question: what is the relationship (effect or association) of higher coffee consumption with health outcomes in people with type 2 diabetes?

The Committee aimed to distinguish between short-term and long-term effects or associations where possible.

2.2 Nutritional topics

The Committee searched for studies into coffee consumption, which could be either caffeinated or decaffeinated (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.

2.3 Outcomes

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

Surrogate outcomes:

- Glycated haemoglobin (HbA1c);
- Fasting blood glucose;
- Body weight;
- Systolic blood pressure;
- Low-density lipoprotein (LDL) cholesterol;
- Estimated glomerular filtration rate (eGFR).

Long-term health outcomes:

- All-cause mortality;
- Morbidity and/or mortality from total cardiovascular disease (CVD), coronary heart disease (CHD), stroke, heart failure, chronic obstructive pulmonary disease, total cancer, breast cancer, colorectal cancer, lung cancer, dementia, depression, chronic kidney disease.

Other:

- Diabetes remission: HbA1c <48 mmol/mol and no use of diabetes medication for ≥1 year;
- Diabetes reversion: HbA1c <53 mmol/mol and less medication use for ≥1 year.

For cohort studies, the Committee included only studies with long-term health outcomes.

2.4 Selection and evaluation of literature

A detailed description of the approach used by the Committee for selecting and evaluating scientific literature is provided in the background document *Methodology for the evaluation of evidence*.[6] To summarise, the Committee aimed to base its evaluation of scientific literature on systematic reviews (SRs), including meta-analyses (MAs), of randomised controlled trials (RCTs) and prospective cohort studies (i.e. prospective cohort studies, nested case-control studies and case-cohort studies) examining the effects or associations of an increased intake of coffee with the above-mentioned health outcomes in people with type 2 diabetes. The literature search for SRs and MAs was performed in PubMed and Scopus in February 2021. The search strategies, flow diagram of the literature search and detailed description of the study selection are provided in **Annex A**.

2.4.1 Selection of randomised controlled trials

The Committee only found SRs and MAs of RCTs that addressed acute effects (i.e. effects induced within a few hours after receiving the intervention) of coffee consumption on markers of blood glucose control in people with type 2 diabetes.[7] This does not fit within the inclusion criterion of the Committee and therefore those SRs were not evaluated. No SRs or MAs of RCTs addressing non-acute effects were found. So, literature regarding surrogate outcomes could not be evaluated in the current background document.

2.4.2 Selection of prospective cohort studies

No SRs or MAs of prospective cohort studies were found. Therefore, the Committee additionally searched in existing external dietary guidelines for diabetes[8-13] for literature references of prospective cohort studies addressing the associations of coffee consumption with long-term health outcomes in people with type 2 diabetes.

The Committee retrieved one pooled analysis of prospective cohort studies in which analyses were performed among subgroups of people with diabetes (probably a combination of type 1 diabetes and type 2 diabetes).[14] Furthermore, the Committee found five individual prospective cohort studies that were performed in cohorts of people with type 2 diabetes.[15-19] In addition, four individual prospective cohort studies were found in which a subgroup analysis was performed among people with

diabetes (probably a combination of type 1 diabetes and type 2 diabetes).[20-23] Four of those studies[14,21-23] reported only on all-cause mortality whereas the other six studies reported also on cause-specific mortality, i.e. mortality from CVD, CHD, stroke and cancer (Table 1). The Committee did not find prospective cohort studies within the pre-specified in- and exclusion criteria for any of the other specified chronic diseases and diabetes remission or reversion.

Table 1 Overview of prospective cohort studies selected by the Committee for the evaluation of the association of coffee consumption with health outcomes in people with type 2 diabetes.

Health outcome[a]	Pooled analysis (of prospective cohort studies)	Individual prospective cohort studies
All-cause mortality	Sluik et al., 2014[14]	Bidel et al., 2006[15] Zhang et al., 2009[16] Zhang et al., 2009[17] Neves et al., 2018[18] Komorita et al., 2020[19] Van Dongen et al., 2017[20] Freedman et al., 2012[21] Loftfield et al., 2015[22] Loftfield et al., 2018[23]
Morbidity or mortality due to CVD	None	Bidel et al., 2006[15] Zhang et al., 2009[16] Zhang et al., 2009[17] Neves et al., 2018[18] Komorita et al., 2020[19] Van Dongen et al., 2017[20]
Morbidity or mortality due to CHD	None	Bidel et al., 2006[15] Zhang et al., 2009[16] Zhang et al., 2009[17] Van Dongen et al., 2017[20]
Morbidity or mortality due to stroke	None	Bidel et al., 2006[15] Zhang et al., 2009[16] Zhang et al., 2009[17]
Mortality due to cancer	None	Neves et al., 2018[18] Komorita et al., 2020[19]

CHD: coronary heart disease; CVD: cardiovascular disease

[a] The table contains the health outcomes for which (relevant) studies were found. For the health outcomes that are not listed in the table, no (relevant) studies were found.

2.5 Drawing conclusions

A detailed description of the approach used by the Committee to draw conclusions is provided in the background document *Methodology for the evaluation of evidence*.[6] In short, the Committee drew conclusions on (the certainty of) the evidence regarding associations of higher coffee consumption with long-term health outcomes in people with type 2 diabetes, based on the number of studies, number of participants and number of cases that contributed to the evaluation. Also, it took into account the risk of bias and heterogeneity between studies.

The Committee used the decision tree (**Annex B**) as a tool to support consistency in drawing conclusions.

03 associations of coffee consumption

The scientific evidence for associations of coffee consumption with long-term health outcomes in people with type 2 diabetes is described in Table 2.

Table 2 Summary of associations of coffee consumption or caffeine intake from coffee with the risks of all-cause mortality and morbidity or mortality from CVD, CHD, stroke and cancer in people with type 2 diabetes: prospective cohort studies.

Study; Study duration[a]	Sluik et al., 2014[14]; 10 years	Loftfield et al., 2015[22]; 9 years	Loftfield et al., 2018[23]; 7 years	Bidel et al., 2006[15]; 20 years	Zhang et al., 2009[16]; NR; 62,722 person-years
Study design	Pooled analysis of 15 cohorts	Individual cohort study	Individual cohort study	Individual cohort study	Individual cohort study
Cohort name	EPIC	Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial	UK Biobank	NR	NHS
Exposure	Coffee consumption. No information on brewing method was available.	Coffee consumption. Categorised into non-consumption and ≥4 cups/d. No information on brewing method was available.	Coffee consumption. Categorised into 0 cups/d (reference group); <1 cup/d; 1 cup/d; 2-3 cups/d; 4-5 cups/d; and ≥6 cups/d. Six categories of coffee type were asked, including decaffeinated, instant and ground coffee. No information on brewing method was available.	Coffee consumption. Categorised into 0-2 cups/d (reference group); 3-4 cups/d; 5-6 cups/d; and ≥7 cups/d. No information was available on brewing method or on whether or not the coffee was caffeinated.	Caffeinated coffee consumption. Categorised into <1 cup/mo (reference group); 1 cup/mo to 4 cups/wk; 5-7 cups/wk; 2-3 cups/d; and ≥4 cups/d. No information on brewing method was available.
Dietary assessment method	Self-administered, validated, country-specific dietary questionnaire at baseline, either quantitative dietary questionnaires, semi-quantitative FFQs, or combined dietary methods of food records and questionnaires.	FFQ assessed at baseline. The FFQ included a question on consumption of decaffeinated coffee.	Questionnaire (no further details provided) assessed at baseline.	General, self-administered questionnaire assessed at baseline. Not validated for coffee.	Validated semi-quantitative FFQs administered in 1980, 1984, 1986, 1990, 1994, 1998 and 2002.
Number of participants; number of cases	6384 participants; All-cause mortality: 830	~3839 participants; All-cause mortality: NR	26063 participants; All-cause mortality: 1880	3837 participants; All-cause mortality: 1471 CVD mortality: 909 CHD mortality: 598 Stroke mortality: 210	7170 participants; All-cause mortality: 734 CVD incidence: 658 CHD incidence: 434 Stroke incidence: 224

Study; Study duration[a]	Sluik et al., 2014[14]; 10 years	Loftfield et al., 2015[22]; 9 years	Loftfield et al., 2018[23]; 7 years	Bidel et al., 2006[15]; 20 years	Zhang et al., 2009[16]; NR; 62,722 person-years
Strength of the association: HR (95%CI) per category of coffee consumption	ALL-CAUSE MORTALITY: Per 100 g/d higher intake: 0.99 (0.97-1.01)	ALL-CAUSE MORTALITY: ≥4 cups/d vs. none: 0.76 (0.60, 0.97)	ALL-CAUSE MORTALITY: <1 vs. 0: 0.89 (0.73-1.09) 1 vs. 0: 0.91 (0.79-1.05) 2-3 vs. 0: 0.86 (0.75-0.98) 4-5 vs. 0: 0.82 (0.69-0.96) ≥6 vs. 0: 0.88 (0.72-1.06) P-trend 0.06	ALL-CAUSE MORTALITY: 3-4 vs. 0-2: 0.77 (0.65-0.91) 5-6 vs. 0-2: 0.68 (0.58-0.80) ≥7 vs. 0-2: 0.70 (0.59-0.85) P-trend <0.001 CVD MORTALITY: 3-4 vs. 0-2: 0.79 (0.64-0.97) 5-6 vs. 0-2: 0.70 (0.57-0.86) ≥7 vs. 0-2: 0.71 (0.56-0.90) P-trend 0.006 CHD MORTALITY: 3-4 vs. 0-2: 0.78 (0.60-1.01) 5-6 vs. 0-2: 0.70 (0.54-0.90) ≥7 vs. 0-2: 0.63 (0.47-0.84) P-trend 0.01 STROKE MORTALITY: 3-4 vs. 0-2: 0.77 (0.50-1.19) 5-6 vs. 0-2: 0.64 (0.41-0.99) ≥7 vs. 0-2: 0.90 (0.56-1.45) P-trend 0.12	ALL-CAUSE MORTALITY: 4/wk vs. <1/mo: 0.69 (0.47-1.02) 5-7/wk vs. <1/mo: 0.89 (0.63-1.26) 2-3/d vs. <1/mo: 0.71 (0.47-1.06) ≥4/d vs. <1 mo: 0.80 (0.41-1.54) P-trend 0.45 CVD INCIDENCE[c]: 4/wk vs. <1/mo: 1.04 (0.80-1.36) 5-7/wk vs. <1/mo: 1.14 (0.91-1.44) 2-3/d vs. <1/mo: 0.92 (0.70-1.20) ≥4/d vs. <1 mo: 0.76 (0.50-1.14) P-trend 0.09 CHD INCIDENCE[c]: 4/wk vs. <1/mo: 0.94 (0.67-1.30) 5-7/wk vs. <1/mo: 1.14 (0.86-1.50) 2-3/d vs. <1/mo: 0.80 (0.57-1.12) ≥4/d vs. <1 mo: 0.70 (0.43-1.14) P-trend 0.06 NON-FATAL MI: 0.74 (0.38-1.45); P-trend 0.38 CHD MORTALITY: 0.67 (0.33-1.36); P-trend 0.07 STROKE INCIDENCE[c]: 4/wk vs. <1/mo: 1.24 (0.80-1.93) 5-7/wk vs. <1/mo: 1.13 (0.76-1.70) 2-3/d vs. <1/mo: 1.16 (0.73-1.85) ≥4/d vs. <1 mo: 0.86 (0.40-1.84) P-trend 0.74
Study population	People with a confirmed diagnosis of diabetes (type 1 or 2); BMI[a]: 29 ± 5 kg/m^2; diabetes duration: NR; diabetes medication: NR; men and women; Europe	People with self-reported diabetes; type of diabetes: NR; BMI: NR; diabetes duration: NR; diabetes medications: NR; men and women; USA	People diagnosed with diabetes; type of diabetes: NR; BMI: NR; diabetes duration: NR; diabetes medications: NR; men and women; Europe	People diagnosed with type 2 diabetes; BMI[a]: 29 to 30 kg/m^2; diabetes duration[a]: NR; diabetes medications[b]: NR; men and women; Europe	People diagnosed with type 2 diabetes; BMI[a]: 28 to 31 kg/m^2; diabetes duration[a]: NR; diabetes medications[b]: NR; women; USA

Study; Study duration[a]	Zhang et al., 2009[17]; NR; 24,121 person-years	Neves et al., 2018[18]; 5 years	Komorita et al., 2020[19]; 5 years	Van Dongen et al., 2017[20]; 7 years	Freedman et al., 2012[21]; 14 years
Study design	Individual cohort study	Individual cohort study	Individual cohort study	Individual cohort study	Individual cohort study
Cohort name	HPFS	NHANES	Fukuoka Diabetes Registry	Alpha Omega Cohort	NIH–AARP Diet and Health Study
Exposure	Caffeinated coffee consumption. Categorised into <1 cup/mo (reference group); 1 cup/mo to 4 cups/wk; 5-7 cups/wk; 2-3 cups/d; and ≥4 cups/d. No information on brewing method was available.	Caffeine intake from coffee. Categorised into no (reference group); <100 mg/d; 100 to <200 mg/d; and ≥200 mg/d. Particularly paper filtered coffee was consumed.	Coffee consumption. Categorised into none (reference group); ≤1 cup/d; 1 cup/d; and ≥2 cups/d. No information was available on brewing method or on whether or not the coffee was caffeinated.	Coffee consumption. Categorised into 0-2 cups/d (reference group); >2-4 cups/d; and >4 cups/d. No information on brewing method was available.	Coffee consumption. Categorised into 0 cups/d; <1 cup/d; 1 cup/d; 2 or 3 cups/d; and ≥4 cups/d.
Dietary assessment method	Validated semi-quantitative FFQs administered in 1986, 1990, 1994, 1998 and 2002.	One or two 24-hour dietary recalls.	Validated self-administered brief diet history questionnaire assessed at baseline.	Validated FFQ assessed at baseline. The FFQ included questions on different coffee preparations, including caffeinated coffee and decaffeinated coffee.	Validated questionnaire, assessed at baseline.
Number of participants; number of cases	3497 participants; All-cause mortality: 538 CVD incidence: 435 CHD incidence: 342 Stroke incidence: 111	*WOMEN*: 1974 participants; All-cause mortality: 351 CVD mortality: 79 Cancer mortality: 54 *MEN*: 1974 participants; All-cause mortality: 407 CVD mortality: 120 Cancer mortality: 79	4923 participants; All-cause mortality: 309 CVD mortality: 76 Cancer mortality: 114	884 participants; All-cause mortality: 240 CVD mortality: 108 IHD mortality: 68	*WOMEN*: 2490 participants; All-cause mortality: NR *MEN*: 5144 participants; All-cause mortality: NR
Strength of the association: HR (95%CI) per category of coffee consumption	ALL-CAUSE MORTALITY: 4/wk vs. <1/mo: 0.69 (0.47-1.02) 5-7/wk vs. <1/mo: 0.89 (0.63-1.26) 2-3/d vs. <1/mo: 0.71 (0.47-1.06) ≥4/d vs. <1 mo: 0.80 (0.41-1.54) P-trend 0.45	ALL-CAUSE MORTALITY: *WOMEN:* <100 vs. 0 mg: 0.74 (0.53-1.02) 100-200 vs. 0 mg: 0.71 (0.46-1.09) ≥200 vs. 0 mg: 0.53 (0.35-0.80) P-trend 0.004 *MEN:* <100 vs. 0 mg: 1.04 (0.74-1.47) 100-200 vs. 0 mg: 0.76 (0.53-1.08) ≥200 vs. 0 mg: 1.09 (0.76-1.56) P-trend 0.873	ALL-CAUSE MORTALITY: ≤1 vs. 0: 0.88 (0.66-1.18) 2-3 vs. 0: 0.81 (0.58-1.13) ≥4 vs. 0: 0.59 (0.42-0.82) P-trend 0.002	ALL-CAUSE MORTALITY: >2-4 vs. 0-2: 1.13 (0.79-1.61) >4 vs. 0-2: 1.24 (0.85-1.80)	ALL-CAUSE MORTALITY: *WOMEN:* <1 vs. 0: 1.08 (0.95-1.24) 1 vs. 0: 0.90 (0.78-1.03) 2-3 vs. 0: 0.92 (0.81-1.04) ≥4 vs. 0: 0.86 (0.73-1.02) P-trend 0.01 *MEN:* <1 vs. 0: 0.99 (0.88-1.11) 1 vs. 0: 0.92 (0.82-1.03) 2-3 vs. 0: 0.85 (0.77-0.95) ≥4 vs. 0: 0.81 (0.72-0.91) P-trend <0.001

Study; Study duration[a]	Zhang et al., 2009[17]; NR; 24,121 person-years	Neves et al., 2018[18]; 5 years	Komorita et al., 2020[19]; 5 years	Van Dongen et al., 2017[20]; 7 years	Freedman et al., 2012[21]; 14 years
Strength of the association: HR (95%CI) per category of coffee consumption -continued	CVD INCIDENCE[c]: 4/wk vs. <1/mo: 0.77 (0.53-1.10) 5-7/wk vs. <1/mo: 0.93 (0.67-1.28) 2-3/d vs. <1/mo: 0.66 (0.45-0.97) ≥4/d vs. <1 mo: 0.88 (0.50-1.57) P-trend 0.29 CHD INCIDENCE[c]: 4/wk vs. <1/mo: 0.63 (0.41-0.97) 5-7/wk vs. <1/mo: 0.90 (0.62-1.31) 2-3/d vs. <1/mo: 0.66 (0.42-1.02) ≥4/d vs. <1 mo: 0.81 (0.41-1.62) P-trend 0.45 STROKE INCIDENCE[c]: 4/wk vs. <1/mo: 1.15 (0.58-2.27) 5-7/wk vs. <1/mo: 0.97 (0.51-1.86) 2-3/d vs. <1/mo: 0.63 (0.29-1.36) ≥4/d vs. <1 mo: 0.97 (0.33-2.85) P-trend 0.31	CVD MORTALITY: *WOMEN:* <100 vs. 0 mg: 0.96 (0.56-1.66) 100-200 vs. 0 mg: 0.72 (0.28-1.85) ≥200 vs. 0 mg: 0.42 (0.14-1.25) P-trend 0.11 *MEN:* <100 vs. 0 mg: 1.33 (0.79-2.26) 100-200 vs. 0 mg: 0.70 (0.35-1.41) ≥200 vs. 0 mg: 0.97 (0.44-2.15) P-trend 0.56 CANCER MORTALITY: For the highest versus lowest category (≥200 versus 0 mg/d): *WOMEN:* 0.59 (0.15-2.39); P-trend 0.39 *MEN:* 2.24 (1.10-4.56); P-trend 0.27	CVD MORTALITY: ≤1 vs. 0: 0.92 (0.51-1.65) 2-3 vs. 0: 0.83 (0.42-1.62) ≥4 vs. 0: 0.53 (0.27-1.04) P-trend 0.06 CANCER MORTALITY: For the highest versus lowest category (≥2 cups/d versus none): 0.78 (0.45-1.34); P-trend 0.41	CVD MORTALITY: >2-4 vs. 0-2: 0.75 (0.45-1.26) >4 vs. 0-2: 0.95 (0.56-1.60) IHD MORTALITY: >2-4 vs. 0-2: 1.00 (0.52-1.93) >4 vs. 0-2: 0.86 (0.43-1.73)	
Study population	People diagnosed with type 2 diabetes; BMI[a]: NR; diabetes duration[a]: NR; diabetes medications[b]: NR; men; USA	People diagnosed with type 1 or type 2 diabetes, percentage of type 1 diabetes NR; BMI[a]: 34 to 35 (women), 31 to 32 (men) kg/m^2; diabetes duration[a]: 3 to 7 y (women), 3 to 5 y (men); diabetes medications[b]: insulin, NR on oral agents use; men and women; USA	People diagnosed with type 2 diabetes; BMI[a]: 24 kg/m^2; diabetes duration[a]: 15 to 16 y; diabetes medications[b]: oral agents, insulin; men and women; Japan	People with a prior MI, and diagnosed with diabetes; type of diabetes: NR; BMI[a]: NR; diabetes duration[a]: NR; diabetes medications[b]: NR; men and women; Europe	People diagnosed with diabetes; type of diabetes: NR; BMI: NR; diabetes duration: NR; diabetes medications: NR; men and women; USA

BMI: body mass index; CI: confidence interval; CHD: coronary heart disease; CVD: cardiovascular disease; d: day; EPIC: European Prospective Investigation into Cancer and Nutrition; FFQ: food frequency questionnaire; HR: hazard ratio; HPFS: Health Professionals Follow-up Study; IHD: ischaemic heart disease; MI: myocardial infarction; mo: months; NHANES: National Health and Nutrition Examination Survey; NHS: Nurses' Health Study; NIH-AARP: National Institutes of Health-American Association of Retired Persons; NR: not reported; USA: United States of America; wk: weeks; y: years.

[a] Those values represent the average or median duration/BMI.

[b] Diabetes medications represent the types of medications that were used among the participants (it does not mean that all participants used those medications).

[c] Fatal and non-fatal events combined.

The Committee concluded the following:

Prospective cohort studies show that a relatively higher coffee consumption is associated with a lower risk of all-cause mortality in people with type 2 diabetes. The evidence is limited.

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

1. There are no MAs that address associations of coffee consumption with the risk of all-cause mortality. There is one pooled analysis of 15 cohorts, with more than 500 cases of mortality, and there are nine individual prospective cohort studies, that address this topic. In total, more than 500 mortality cases were reported, which is the first step required to mark the evidence as strong. However, there were other considerations leading to the conclusion with limited evidence, as described below.
2. There is little heterogeneity in direction of associations between the ten studies. The pooled analysis shows no (statistically significant) association between coffee consumption and the risk of all-cause mortality. Of the individual studies, five show a statistically significant inverse association and three show a non-significant inverse association, i.e. reduced risks of all-cause mortality for higher coffee consumption. Only the study by Van Dongen et al.[20] reported an (non-significant) increased risk of all-cause mortality for higher coffee consumption. This study was performed among persons with a history of myocardial infarction (and diabetes), which might be an explanation for the observed heterogeneity.
3. There is moderate heterogeneity in size of the association and the Committee found it difficult to give a (specific) explanation for this. Differences in reference categories between studies, preparation method of consumed coffee, baseline (habitual) coffee intake and type of diabetes (type 1 or 2) might be causes of the heterogeneity. However, too little information was available in most studies to examine these hypotheses. Whether the consumed coffee included only caffeinated coffee or was a combination of decaffeinated and caffeinated coffee is likely not a source of heterogeneity. Also the categorisation of coffee consumption used for analysis differed between studies, which makes comparisons of results between studies difficult. The Committee noted that a lower risk of all-cause mortality is generally observed for higher coffee consumption categories and not for categories of less than 2 cups a day. Overall, due to the null-association in the pooled analysis and the partially unexplained heterogeneity, the Committee considered the evidence limited.

Prospective cohort studies show that consumption of 2 to 4 cups of coffee a day compared to none or very little coffee consumption is associated with a 20 to 30% lower risk of morbidity or mortality due to CVD in people with type 2 diabetes. The evidence is strong.

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

1. There are no MAs that address associations of coffee consumption with the risk of morbidity or mortality from CVD. There are six individual prospective cohort studies, with in total >500 cases, that address this topic. This is the first step required to mark the evidence as strong.
2. There is no heterogeneity in direction of associations between the six studies: all reported reduced risks of CVD for higher coffee consumption. Three studies reported a (borderline) statistically significant decreasing trend in risk of cardiovascular morbidity or mortality and one study showed a statistically significant reduced risk of CVD for 2-3 cups of coffee a day compared to less than 1 cup a month (all in cohorts that were comprised of solely type 2 diabetes patients). The two studies that reported non-significant associations were smaller in terms of number of participants and number of cases, which could be an explanation for the lack of significance. In addition, those studies may include people with type 1 diabetes, although the proportion of people with type 1 diabetes is expected to be low.
3. There is moderate heterogeneity in size of the association, which may be explained by the differences in reference categories between studies and preparation method of consumed coffee. Whether the consumed coffee included only caffeinated coffee or was a combination of decaffeinated and caffeinated coffee is likely not a source of heterogeneity. Overall, the Committee judged that there is little heterogeneity or heterogeneity could be explained and that there were no major other considerations. This led to the conclusion with strong evidence.

Prospective cohort studies show that a relatively higher consumption of coffee is associated with lower risk of morbidity or mortality due to CHD in people with type 2 diabetes. The evidence is limited.

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

1. There are no MAs that address associations of coffee consumption with risk of morbidity or mortality from CHD. There are four individual prospective cohort studies, with in total >500 cases, that address this topic, which excludes a conclusion with strong evidence (for which at least five studies are required).
2. There is no heterogeneity in direction of associations between the four studies: all reported reduced risks of CHD for higher coffee consumption. Two studies reported (borderline) statistically significant associations (both in cohorts that were comprised of solely type 2 diabetes patients) and two studies reported non-significant

associations. One study that reported no statistically significant association was smaller in terms of number of participants and number of cases, which could be an explanation for the lack of significance. Also, this study was comprised of participants who had both diabetes and prior myocardial infarction. In the other study, relatively few CHD cases contributed to the category of ≥4 cups of coffee a day, which may have contributed to the lack of association in this category.

3. There was moderate heterogeneity in size of the association, which may be explained by the differences in reference categories between studies and preparation method of consumed coffee. Whether the consumed coffee included only caffeinated coffee or was a combination of decaffeinated and caffeinated coffee is likely not a source of heterogeneity. Overall, the Committee considered the evidence as limited.

There is too little research to draw conclusions regarding associations of coffee consumption with the risk of morbidity or mortality due to stroke in people with type 2 diabetes.

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

1. There are no MAs that address associations of coffee consumption with risk of morbidity or mortality from stroke. There are three individual cohort studies, with a total of >500 cases, that address this topic, which excludes a conclusion with strong evidence (for which at least five studies are required).
2. All three cohort studies reported no statistically significant association between coffee consumption and stroke risk. Three studies is too few to allow a conclusion of ‘an association is unlikely’. Therefore, the Committee concludes that too little research is available to draw a conclusion.

There is too little research to draw conclusions regarding associations of coffee consumption with the risk of mortality due to cancer in people with type 2 diabetes.

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

There are no MAs that address associations of coffee consumption with risk of mortality due to cancer. There are only two individual prospective cohort studies that address this topic. That is too little evidence to base conclusions on.

Explanation:

The Committee included one pooled analysis of 15 cohorts in the evaluation of the association of coffee consumption with the risk of all-cause mortality in people with diabetes. Furthermore, nine individual prospective cohort studies were identified that investigated this association in (subgroups of) people with (type 2) diabetes. Those studies also addressed the outcomes of morbidity or mortality due to CVD, CHD

and stroke, morbidity from myocardial infarction, and cancer mortality. All evaluations are of long-term associations (longer than one year). The studies are further explained below.

The study by **Sluik et al.**[14] is a pooled analysis of 15 cohorts from six European countries from the European Prospective Investigation into Cancer and Nutrition (EPIC) consortium, covering six European countries. For this study, almost 6400 participants with a confirmed diagnosis of diabetes were included. No information was provided on the proportions of the study population that had type 1 diabetes and type 2 diabetes. After a median of 9.9 years of follow-up (interquartile range (IQR): 8.8 to 11.0 years), 830 cases of all-cause mortality were reported. Mortality data was ascertained by various methods, depending on the country and included, for example, record links with cancer registries and follow-up mailings to participants. Coffee consumption was assessed at baseline using self-administered, validated, country-specific dietary questionnaires. In data analyses, coffee consumption was assessed continuously and analyses were adjusted for many potential confounding factors, such as sex, physical activity, smoking status and diabetes medication.

Median (IQR) coffee consumption at baseline among individuals with diabetes was 487 (211-664) g/d. No association of coffee consumption with risk of all-cause mortality was observed (HR per 100 g/d higher intake 0.99, 95%CI 0.97-1.01). Sensitivity analyses showed that excluding participants with comorbidities at baseline or excluding energy misreporters did not substantially affect the risk estimates. Among the non-diabetic participants from this cohort, higher coffee consumption was associated with a lower risk of all-cause mortality (HR 0.98, 95%CI 0.97-0.98), although two different tests for interaction with baseline diabetes status indicated that no statistically significant interaction was present.

Strengths of this study include the large sample size, the verification of diabetes diagnosis and the use of validated dietary questionnaires to estimate coffee intake. A limitation of the study is that persons with type 1 and type 2 diabetes were combined in the analyses and it is unknown what proportion of the study population had type 2 diabetes. Furthermore, the level of heterogeneity between studies was not reported. A third limitation is that no distinction was made between caffeinated and non-caffeinated coffee and that no information on brewing method was provided. Last, associations between coffee consumption and cause-specific mortality were not examined.

The study by **Loftfield et al. (2015)**[22] was performed among male and female participants of a large, population-based randomised cancer screening trial, with ten participating study centres across the USA. Participants with a history of cancer prior to dietary assessment and participants with a history of CVD were excluded from the current study.

Of those remaining, approximately 3939 participants reported having diabetes (type unknown). Mean follow-up was 9 years. Mortality data was obtained from annual mailed questionnaires and linkage to the National Death Index. The number of participants that had died during follow-up was not reported for the subgroup of diabetes patients.
Coffee consumption was assessed at baseline with a food frequency questionnaire (FFQ; reflecting the previous 12 months). The FFQ was based on two validated FFQs.[24] For the analyses in the subgroup of diabetes patients, coffee consumption was categorised into consumption of 0 cups of coffee a day (non-coffee drinkers; reference) and ≥4 cups a day. Associations of coffee consumption with mortality risk were adjusted for many potential confounding variables, such as age, sex, detailed smoking history, educational level and total energy intake.

The average coffee consumption of the study population was not reported. Compared to non-coffee drinkers, participants consuming ≥4 cups of coffee a day were at lower risk of (all-cause) mortality (HR 0.76, 95%CI 0.60-0.97).

A strength of this study is the large sample size. A limitation of the study is that results were presented only for those consuming ≥4 cups of coffee a day compared to non-coffee drinkers. The first group is rather broad and information on those consuming >0 to <4 cups of coffee a day is lacking. This limits the possibility to determine if lesser frequency of coffee consumption showed a similar association. Also, no distinction was made between caffeinated and non-caffeinated coffee in the subgroup of diabetes patients and no information on brewing method was provided. In addition, it is unknown what proportion of the diabetes population had type 2 diabetes. Last, associations between coffee consumption and the risk of *c*ause-specific mortality were not examined.

The study by **Loftfield et al. (2018)**[23] included participants of the UK Biobank. Of those, 26063 participants were diagnosed with diabetes, of whom 1880 died during the 7-year follow-up. Coffee consumption was assessed with a baseline questionnaire. No details were provided by the authors on the validity of the questionnaire. Information on mortality was obtained from National Health Service registries. For the data analyses, coffee consumption was categorised into 0; <1; 1; 2 to 3; 4 to 5; and 6 cups a day. The association of coffee with risk of mortality was adjusted for multiple potential confounders, such as age, sex, smoking, BMI, alcohol consumption and physical activity.

In the full UK Biobank cohort, 22% participants were non-coffee drinkers. Among coffee drinkers, 56%, 23% and 19% reported usually drinking instant, ground and decaffeinated coffee, respectively. Among people with diabetes, a borderline significant decreasing trend in (all-cause) mortality over the categories of coffee consumption was observed. Compared to non-consumers of coffee, those consuming 2-3 or 4-5 cups of coffee a

day had a lower risk of all-cause mortality (HR 0.86, 95%CI 0.75-0.98 and HR 0.82, 95% CI 0.69-0.96, respectively). There was no statistically significant association of consuming 6 or more cups of coffee a day compared to no coffee consumption (HR 0.88, 95%CI 0.72-1.06).

A strength of the study is the large sample size. A limitation is that the validity of the questionnaire for measuring coffee intake was not reported. In addition, it is unknown what proportion of the diabetes population had type 2 diabetes. Another limitation is that associations of coffee consumption with cause-specific mortality were not examined. Also, no information on brewing method was provided.

The study by **Bidel et al.**[15] evaluated the association of coffee consumption with risks of mortality from all causes, CVD, CHD and stroke. The study included 3837 Finnish men and women diagnosed with type 2 diabetes. During a mean follow-up of 20 years, 1471 participants had died, of whom 909 from CVD, 598 from CHD and 210 from stroke. Mortality data was obtained from Statistics Finland. Coffee consumption was assessed at baseline using a general questionnaire. That questionnaire contained a few diet-related questions. The validity of the questionnaire for measuring coffee consumption was not assessed. For the data analyses, daily coffee consumption was categorised into 0-2 cups; 3-4 cups; 5-6 cups; and ≥7 cups. The associations were adjusted for a range of potential confounders, such as age, sex, body mass index (BMI), education level and smoking status.

Median daily coffee was 5 cups (IQR 3-6 cups). Compared to participants consuming 0-2 cups of coffee per day, participants consuming 3-4, 5-6 and ≥7 cups of coffee per day all had a lower risk of all-cause mortality and CVD mortality. Also, there was a statistically significant decreasing linear trend in the risks of all-cause mortality and CVD mortality (HR for the highest versus lowest category 0.70, 95%CI 0.59-0.85; P-trend <0.001 and HR 0.71, 95%CI 0.56-0.90; P-trend 0.006, respectively). In addition, there was a lower risk of CHD within all categories of coffee consumption compared to the reference group of 0-2 cups a day (borderline significant for the category of 3-4 cups of coffee), with a decreasing trend over the categories of coffee consumption (HR for the highest versus lowest category 0.63, 95%CI 0.47-0.84; P-trend 0.01). The associations with the risks of all-cause mortality, CVD mortality and CHD mortality were very comparable for men and women. There was no association with the risk of stroke mortality for the highest versus lowest category of coffee consumption. However, there was a lower risk of stroke mortality in participants consuming 5-6 cups of coffee per day compared to 0-2 cups (HR 0.64, 95%CI 0.41-0.99).

A strength of the study is the relatively high number of mortality events, which benefits to the power of the data analyses to detect associations. A limitation of the study is that the questionnaire used to assess coffee consumption was not validated and there was no information on whether the coffee contained caffeine and on whether the coffee was filtered. Moreover, the duration and the severity of diabetes and the type of treatment used for management of diabetes were unknown and could therefore not be taken into account in the data analyses.

Two cohort studies published by **Zhang et al.** were included by the Committee. One was performed among women of the Nurses' Health Study (NHS)[16] and the other among men of the Health Professionals Follow-up Study (HPFS).[17] Both used repeated validated FFQs to assess 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. Diagnoses of CVD, CHD and stroke were obtained from medical records. Deaths were reported by next of kin or the postal system or ascertained through the National Death Index.

For the data analyses, coffee consumption was categorised into <1 cup/month (reference group); 1 cup/month to 4 cups/week; 5-7 cups/week; 2-3 cups/day; and ≥4 cups/day. The analyses were adjusted for a range of potential confounding variables, such as age, smoking status, alcohol intake, physical activities and total energy intake.

There were 7170 women diagnosed with type 2 diabetes included in the NHS analyses, with 62,722 person-years of follow-up. In total, 734 women had died during follow-up, and 658 had experienced a CVD event, 434 a CHD event and 224 a stroke event. The average coffee consumption in the study population was not reported. The category of 5-7 cups of coffee per week had the highest contribution of person-years. The women particularly consumed paper-filtered coffee. Compared to women consuming less than one cup of coffee a month, women consuming ≥4 cups of coffee a day had lower risks of all-cause mortality, incident CVD and incident CHD, but this was not statistically significant (HR 0.80, 95%CI 0.55-1.14, HR 0.76, 95%CI 0.50-1.14 and HR 0.70, 95%CI 0.43-1.14, respectively). Also, there was a reducing linear trend over the categories of coffee consumption, but this was not statistically significant (P-values for linear trend were 0.05 for all-cause mortality, 0.09 for incident CVD and 0.06 for incident CHD). Separate associations for fatal CHD and non-fatal CHD (myocardial infarction) showed a slightly stronger reducing association of higher coffee consumption with fatal CHD (HR for ≥4 cups/day versus <1 cup/month 0.67, 95%CI 0.33-1.36; P-trend 0.07) than for non-fatal CHD (HR 0.74, 95%CI 0.38-1.45; P-trend 0.38). For stroke risk, for none of the categories of coffee consumption an

association was observed and there was no evidence for a linear trend in stroke risk over the categories of coffee consumption.

A strength of the study is that updated information on coffee consumption and potential confounders was taken into account in the data analyses. A limitation is that the number of women contributing to the highest category of coffee intake was relatively small, limiting the power to detect associations. Moreover, it was not reported whether the coffee was filtered or not.

There were 3497 men diagnosed with type 2 diabetes included in the HPFS analyses, with 24,121 person-years of follow-up. In total, 538 men had died during follow-up, and 435 had experienced a CVD event, 342 a CHD event and 111 a stroke event. The average coffee consumption in the study population was not reported. The category of 5-7 cups of coffee per week had the highest contribution of person-years. No associations between coffee consumption and risk of all-cause mortality were observed (P-trend 0.45). With respect to cause-specific mortality, compared to men consuming less than one cup of coffee a month, men consuming 2-3 cups of coffee a day had a lower risk of CVD (HR 0.66, 95%CI 0.45-0.97) and CHD (HR 0.66, 95%CI 0.42-1.02), whereas this was not observed for men consuming the highest amount of coffee (≥4 cups a day: HR 0.88, 95%CI 0.50-1.57 for CVD and HR 0.81, 95%CI 0.41-1.62 for CHD). It should be noted there were relatively few person-years (n=1289) and cases of CVD (n=19) and CHD (n=14) contributing to the category of ≥4 cups a day, which may have contributed to the lack of an association in this category. For stroke risk, for none of the categories of coffee consumption an association was observed and there was no evidence for a linear trend in stroke risk over the categories of coffee consumption. The authors reported that – similarly to total coffee consumption – decaffeinated coffee consumption was not associated with CVD risk (data not shown).

A strength of the study is that updated information on coffee consumption and potential confounders was taken into account in the data analyses. A limitation is that the number of men contributing to the highest category of coffee intake was small, limiting the power to detect associations. Moreover, it was not reported whether the coffee was filtered.

The study by **Neves et al.**[18] evaluated the association of caffeine intake from coffee with mortality from CVD and cancer. This study differed from the other studies in this evaluation in that the exposure was the intake of caffeine from coffee and not coffee consumption itself. The Committee judged that this study was relevant for this advisory report, because it specifically addresses caffeine from coffee (and not from other sources such as tea or soft drinks) which makes it likely that it is highly correlates with (caffeinated) coffee consumption. Moreover, two other studies in this evaluation specifically addressed caffeinated coffee consumption (and thus disregarded decaffeinated coffee).

The study included 1974 men and 1974 women from the USA diagnosed with type 1 or type 2 diabetes. No information was provided on the proportions of the study population that had type 1 and type 2 diabetes. Mortality data was obtained from National Death Index public-access files. Caffeine consumption was assessed at baseline with one or two 24-hour dietary recalls. For the data analyses, daily caffeine intake from coffee was categorised into none; <100; 100 to <200; and ≥200 mg/day. According to the Netherlands Nutrition Centre, one cup of coffee contains 60 to 85 mg caffeine, thus the highest category of caffeine consumption concerns approximately 2.5 or more cups of coffee. The associations were adjusted for many potential confounding factors, such as age, annual family income, smoking status, alcohol consumption and diagnosis of hypertension. Data for men and women were analysed separately since there was a significant interaction between sex and caffeine consumption with respect to mortality.

During a median follow-up of 5 years, 351 women had died, of whom 79 from CVD and 54 from cancer. The average daily coffee or caffeine consumption was not reported. The majority of women contributed to the category of <100 mg of caffeine per day (n=979). For all-cause mortality, a statistically significant association was observed for ≥200 mg/day of caffeine intake from coffee (HR 0.53, 95%CI 0.35-0.80), but not for the lower intake categories. With respect to CVD mortality, compared to non-consumers, women in all categories of caffeine intake from coffee did not statistically differ in their risk of CVD mortality. The HR in the highest category (≥200 mg/day) was 0.42 (95%CI 0.14-1.25). There contributed 217 women and 5 cases to this category, which may have limited statistical power to detect an association. There was a tendency towards a reducing trend in the risk of CVD mortality (P-value for linear trend 0.11, and HR per 100 mg/d caffeine from coffee consumption 0.81, 95%CI 0.64-1.02). There was no association of caffeine from coffee consumption with risk of cancer (HR for the highest versus lowest category 0.59, 95%CI 0.15-2.39; P-value for linear trend 0.39).

During a median follow-up of 5 years, 407 men had died, of whom 120 from CVD and 79 from cancer. Among men, there was no association of caffeine from coffee consumption with risk of all-cause mortality (HR for the highest versus lowest category 1.09, 95%CI 0.76-1.56; P-trend 0.87) and CVD mortality (HR 0.97, 95%CI 0.44-2.15; P-trend 0.56). There was a higher risk of cancer mortality in all categories of caffeine intake from coffee compared to no intake. The HRs were not very different across the categories (<100 mg/day: HR 2.51, 95%CI 1.10-5.71; 100 to <200 mg/day: HR 2.19, 95%CI 1.00-4.81; ≥200 mg/day: HR 2.24, 95%CI 1.10-4.56) and there was no linear trend visible over the categories of caffeine intake from coffee (P-value 0.27). No explanation for the higher cancer mortality risk was given.

A strength of the study includes that it was reported that particularly filtered coffee was consumed, whereas in the other studies no information was provided on whether the consumed coffee was filtered or not. Limitations are that type 1 and type 2 diabetes were combined in the analyses and that it is unknown what proportion of the study population had type 2 diabetes. Also, a limited number of 24-hour diet recalls was used to assess coffee consumption. Therefore, the estimated coffee consumption may not fully represent the habitual coffee consumption. It is furthermore unknown if the participants were specifically asked whether the coffee consumed was caffeinated (as caffeine intake was based on reported coffee consumption). Therefore, the Committee could not ascertain that the level of caffeine intake fully corresponds to the level of coffee consumption. Finally, the number of deaths that occurred in the subgroups of men and women was relatively small, limiting the power to detect associations.

The study by **Komorita et al.**[19] evaluated the association of coffee consumption with risks of mortality from CVD and cancer. The study included 4923 Japanese men and women diagnosed with type 2 diabetes. During a mean follow-up of 5 years, 309 participants had died, of whom 76 from CVD and 114 from cancer. It was not reported where mortality data was obtained from. The causes of death were determined based on medical records or death certificates. Coffee consumption was assessed at baseline using a brief validated diet history questionnaire. The relative validity of the questionnaire (using semi-weighed dietary records as reference method) for measuring coffee consumption was high (*r* 0.87 in women and 0.85 in men). For the data analyses, daily coffee consumption was categorised into none; ≤1; 1; and ≥2 cups/day. The associations were adjusted for a range of potential confounders, such as age, sex, BMI, current smoking status and systolic blood pressure.

The average coffee consumption of the study population was not reported. The category of ≥2 cups/day contributed the most participants (n=1660). Compared to participants consuming no coffee, participants consuming ≥2 cups of coffee a day had a lower risk of all-cause mortality (HR 0.59, 95%CI 0.42-0.82) and CVD mortality (HR 0.53, 95%CI 0.27-1.04). Additional adjustment for green tea consumption did not substantially modify those risk estimates. There was a borderline statistically significant reducing linear trend in the risks of all-cause mortality and CVD mortality over the categories of coffee consumption, with P-values of 0.002 and 0.06, respectively. There was no association with the risk of cancer mortality.

A strength of the study includes the high relative validity of the questionnaire used to assess coffee consumption. A limitation of the study includes the small number of CVD and cancer deaths, limiting power to detect associations. Moreover, it was not reported whether the coffee was filtered or caffeinated.

The study by **Van Dongen et al.**[20] is a prospective cohort study performed in a cohort of Dutch people who had previously experienced a myocardial infarction (Alpha Omega Cohort). This cohort originates from the Alpha Omega Trial, which ran from 2002 to 2009 and examined the effect of omega-3 fatty acids. After completion of the trial, the cohort was followed up for mortality until January 2013. At baseline (2002-2006), 884 participants were diagnosed with diabetes and the analyses among this subgroup are described here. The type of diabetes was not reported. It is expected that it concerned both type 1 and type 2 diabetes.

During the median 7-year follow-up, 240 diabetes patients had died, of which 108 due to CVD and 68 due to ischaemic heart disease (IHD). Coffee consumption was assessed with a validated FFQ.
The questionnaire included questions on different coffee preparations (e.g. caffeinated or decaffeinated coffee). The brewing method was not asked. However, the authors noted that most coffee consumed in the Netherlands is paper filtered. Information on mortality and causes of death were obtained from the Dutch National Mortality Registry (Statistics Netherlands). For the data analyses, coffee consumption was categorised into 0 to 2 (reference group), >2 to 4, and >4 cups a day. The associations of coffee consumption with mortality risk were adjusted for potential confounders, such as age, BMI, physical activity, smoking status and total energy intake.

The median coffee consumption of the whole study population was 3 cups a day. Consumption of coffee was not associated with all-cause, CVD or IHD mortality among people with diabetes. For example, HRs (95%CI) for the association with CVD mortality were 0.75 (0.45-1.26) for coffee consumption of >2 to 4 cups/day and 0.95 (0.56-1.60) for >4 cups/day as compared to 0-2 cups/day. In comparison, among non-diabetics, there was a lower risk of CVD and IHD mortality with higher coffee consumption.

A strength of the study is the detailed information that was obtained on coffee consumption. A limitation of the study is the small number of participants in the reference group of 0 to 2 cups of coffee. This may have limited the power to detect associations. Another limitation is that the study was performed among post-myocardial infarction patients, which limits comparison with the other cohort studies evaluated in this background document since those were not specifically performed among such patients. The Committee also noted that the observational analyses were conducted within an RCT that aimed to adapt dietary intake (n-3 fatty acids). The observational analyses were conducted over all intervention arms, whereby the associations were adjusted for intervention arm (n-3 fatty acids versus placebo), but the interaction with the intervention arms was not tested. Last, the Committee had some concerns regarding the funding as the original trial was supported by Unilever R&D (industry)

and its involvement in the study was not reported (**Annex C**). Therefore, the impact on the study findings remains unclear.

The study of **Freedman et al.**[21] was performed among male and female participants of the National Institutes of Health-AARP Diet and Health Study. Participants with cancer, heart disease or stroke at baseline were excluded. The current analyses included 5144 male and 2490 female participants with self-reported diabetes (type unknown). Median follow-up was 14 years. Mortality data was obtained from linkage to the Social Security Administration Death Master File, linkage to cancer registries and responses to questionnaires and other mailings. The number of participants that died during follow-up was not reported for the subgroup of diabetes patients. Coffee consumption was assessed using an FFQ at baseline. Among a subgroup of the study population (not diabetes patients per se), the correlation between coffee consumption assessed with the FFQ and with the 24-hour dietary recalls was shown to be 0.80. Coffee consumption was categorised into five categories: none; <1; 1; 2 or 3; and ≥4 cups/day. Associations of coffee consumption with mortality risk were stratified according to sex and adjusted for many potential confounding variables such as age, BMI, level of education, alcohol consumption, number of cigarettes smoked per day and total energy intake.

The average coffee consumption of the diabetic study population was not reported. At baseline, coffee-consuming participants (especially women) less often reported having diabetes compared to non-coffee consuming participants. Compared to male participants that did not consume any coffee, those drinking 2 or 3 cups of coffee a day and those drinking ≥4 cups a day were at lower risk of (all-cause) mortality (HR 0.85, 95%CI 0.77-0.95 and HR 0.81, 95%CI 0.72-0.91), respectively; P-trend <0.001). No association with all-cause mortality was observed for coffee consumption of <1 or 1 cup a day compared to no coffee consumption in men. Among female participants, none of the coffee consumption categories was statistically significantly associated with risk of all-cause mortality as compared to non-consumption of coffee (e.g. HR for <1 cup/d 1.08, 95%CI 0.95-1.24 and HR for ≥4 cups/d 0.86, 95%CI 0.73-1.02). However, there was a significant trend for an inverse association between coffee consumption and risk of all-cause mortality in women (P-trend 0.01).

A strength of this study is the large sample size. A limitation of the study is that no distinction was made between caffeinated and non-caffeinated coffee in the subgroup of diabetes patients, and that no information on brewing method was provided. Furthermore, persons with type 1 and type 2 diabetes were combined in the analyses and it is unknown what proportion of the diabetes population had type 2 diabetes.
Last, associations between coffee consumption and *cause-specific* mortality were not examined.

Except for the study by Van Dongen et al.[20] for which the Committee had some concerns regarding the funding source, the Committee did not expect that funding or author's conflicts of interest have affected the study findings of the studies included in this evaluation (**Annex C**).

04 summary of conclusions

The Committee's conclusions regarding associations of coffee consumption with health outcomes in people with type 2 diabetes are summarised in Table 3.

Table 3 Overview of conclusions regarding associations of coffee consumption with health outcomes in people with type 2 diabetes, based on prospective cohort studies.

Health outcome[a]	Conclusion
All-cause mortality	Limited evidence for an inverse association
Morbidity or mortality due to CVD	Strong evidence for an inverse association
Morbidity or mortality due to CHD	Limited evidence for an inverse association
Morbidity or mortality due to stroke	Too little research
Mortality due to cancer	Too little research

CHD: coronary heart disease; CVD: cardiovascular disease.

[a] The table contains the health outcomes for which (relevant) studies were found. For the health outcomes that are not listed in the table, no (relevant) studies were found.

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annexes

annex A
search strategy, study selection and flow diagram

Systematic reviews including 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 type 2 diabetes. Literature searches were performed in PubMed and Scopus on 1st February 2021 using the following search strategies:

PubMed

(“diabetes mellitus, type 2”[MeSH] OR Diabet*[tiab] OR T2DM[tiab] OR NIDDM[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

KEY (“diabetes mellitus, type 2”) OR TITLE-ABS-KEY (t2dm) OR TITLE-ABS-KEY (niddm) OR TITLE-ABS (“diabetes mellituss, type 2”) OR TITLE-ABS (diabet*) OR TITLE-ABS (t2dm) OR TITLE-ABS (niddm) AND TITLE-ABS (coffee) OR TITLE-ABS(decaffeinated) OR TITLE-ABS(espresso) OR TITLE-ABS(caffeine) AND TITLE-ABS-KEY (“Systematic review”) OR TITLE-ABS-KEY (“Meta-analysis”) OR TITLE-ABS (review) OR TITLE-ABS (meta-analysis) OR TITLE-ABS (metaanalysis) OR TITLE-ABS (“quantitative review”) OR TITLE-ABS (“quantitative overview”) OR TITLE-ABS (“systematic overview”) OR TITLE-ABS (“methodologic review”) OR TITLE-ABS (“methodologic overview”)

Limit: from 2000

In total, 158 publications were found in PubMed and 232 publications in Scopus. After removal of duplicates, 247 publications remained and were screened for title and abstract. A total of 15 publications remained for

full-text assessment, of which none were selected for the Committee's evaluation of coffee consumption.

Prospective cohort studies

One SR included a relevant prospective cohort study.[15] Articles citing this study were searched in PubMed. This yielded four additional relevant cohort studies.[16-19]

The Committee also searched for individual prospective cohort studies on associations of coffee consumption with long-term health outcomes in external dietary guidelines for diabetes of the following organisations:

- Dutch Diabetes Federation (Nederlandse Diabetes Federatie (NDF)), 2020[8]
- European Association for the Study of Diabetes (EASD) & European Society of Cardiology (ESC), 2020[9]
- American Diabetes Association (ADA), 2019[10]
- Diabetes UK, 2018[11]
- Diabetes Canada, 2018[12]
- Swedish Council, 2010[13]

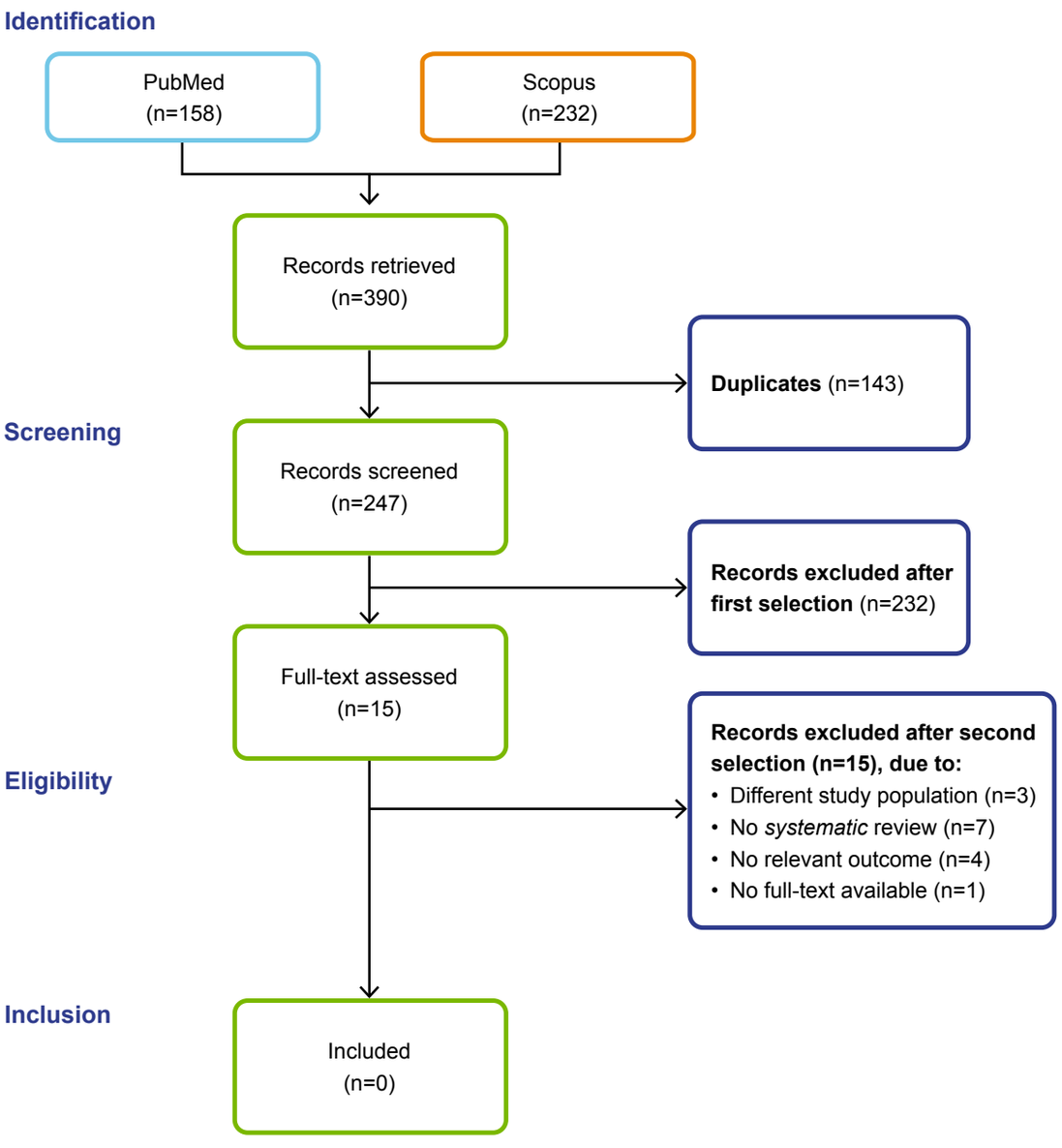
This yielded no other relevant prospective cohort studies.

Via the reference lists of the above-mentioned five cohort studies, the Committee found four additional prospective cohort studies in which a subgroup analysis was performed among diabetes patients (probably a combination of type 1 and type 2 diabetes patients).[20-23] In addition, a pooled analysis that addressed associations for consumption of dairy products and beverages with added sugar also considered coffee consumption.[14]

Altogether, the Committee selected the following ten prospective cohort studies for its evaluation of coffee consumption:

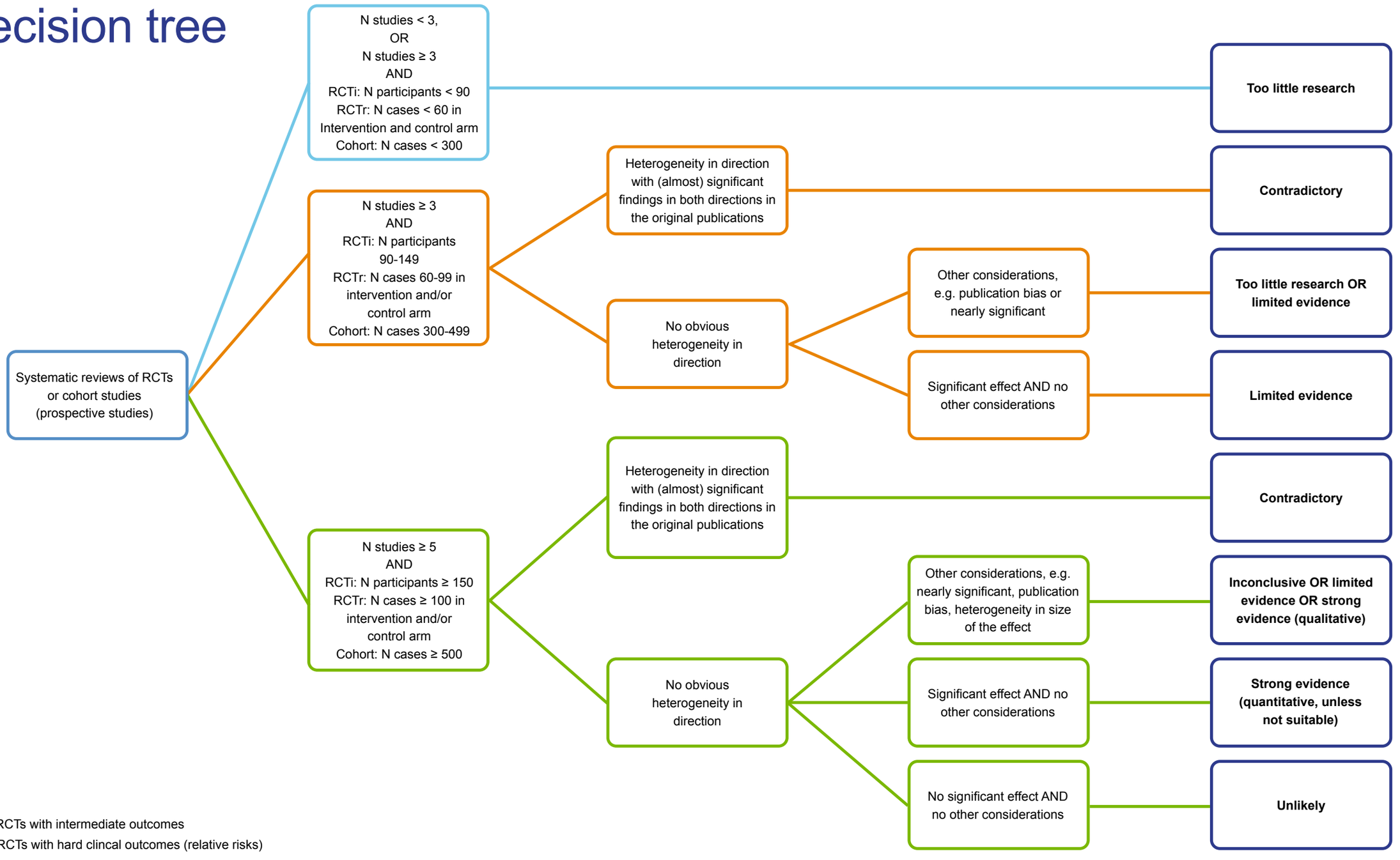
- Sluik et al., 2014[14] (pooled analysis of prospective cohort studies)
- Bidel et al., 2006[15]
- Zhang et al., 2009 (NHS)[16]
- Zhang et al., 2009 (HPFS)[17]
- Komorita et al., 2020 [19]
- Neves et al., 2018[18]
- Van Dongen et al., 2017[20]
- Freedman et al., 2012[21]
- Loftfield et al., 2015[22]
- Loftfield et al., 2018[23]

Flow diagram for the selection of systematic reviews including meta-analyses



annex B

decision tree



RCTi: RCTs with intermediate outcomes
RCTr: RCTs with hard clincal outcomes (relative risks)

annex C

funding sources and conflicts of interest regarding the articles used in this background document

In the table below, the funding sources of the studies listed in this background document and conflicts of interests of authors contributing to those studies are reported.

Study's first author, year	Funding of the work	Conflicts of interest of authors
Bidel, 2006[15]	The study was supported by the Juho Vainio Foundation, the Finnish Foundation for Cardiovascular Research and the Academy of Finland.	The authors declared to have no conflicts of interests.
Freedman, 2012[21]	The study was supported by the National Institutes of Health/National Cancer Institute.	The authors declared to have no conflicts of interests.
Komorita, 2020[19]	The study was supported by the Ministry of Education, Culture, Sports, Science and Technology of Japan.	Two authors were financially supported by the Japan Diabetes Society, one author by the pharmaceutical company Lilly, one author by the Japan Diabetes Foundation and one author by the Japan Heart Foundation and the pharmaceutical companies Astellas and Pfizer. The other authors declared to have no conflicts of interests.
Loftfield, 2015[22]	The study was supported by the National Institutes of Health/National Cancer Institute. One author received a grant from the Yale-National Cancer Institute.	The authors declared to have no conflicts of interests.
Loftfield, 2018[23]	The study was conducted using the UK Biobank resource, which was established by the Wellcome Trust, the Medical Research Council, the UK Department of Health and the Scottish Government, and received (additional) funding from the Welsh Assembly Government, the British Heart Foundation and Diabetes United Kingdom. Furthermore, this study was supported by the National Institutes of Health/National Cancer Institute.	The authors declared to have no conflicts of interests.
Neves, 2018[18]	It was reported that the paper was written without any funding.	The authors declared to have no conflicts of interests.
Sluik, 2014[14]	The study was supported by a European Foundation for the Study of Diabetes (EFSD)/ Sanofi-Aventis grant.	The authors declared to have no conflicts of interests.
Van Dongen, 2017[20]	The Alpha Omega Trial (2002–2009), from which this cohort study emerged, was supported by Netherlands Heart Foundation, the National Heart, Lung and Blood Institute and Office of Dietary Supplements of the National Institutes of Health, Unilever R&D Vlaardingen (industry) and Wageningen University.	The authors declared to have no conflicts of interests.

Study's first author, year	Funding of the work	Conflicts of interest of authors
Zhang, 2009[16] (NHS)	The study was supported by the National Institutes of Health.	The first author was financially supported by the National Natural Science Foundation of China. The other authors declared to have no conflicts of interests.
Zhang, 2009[17] (HPFS)	The study was supported by the National Institutes of Health.	The first author was financially supported by the National Natural Science Foundation of China. The other authors declared to have no conflicts of interests..

HPFS: Health Professionals Follow-up Study; NHS: Nurses' Health Study

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is “to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research...” (Section 22, Health Act).
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.

This publication can be downloaded from www.healthcouncil.nl.

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