Alcohol

No. 2023/02Ie, 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

Contents

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 alcohol 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 alcohol

This background document describes the scientific evidence regarding total ethanol or alcohol intake, further referred to as alcohol intake. It does not distinguish between the alcohol source (e.g., beer, wine, spirit) because such information was generally not available in the evaluated literature. In the Netherlands, one regular glass of an alcoholic beverage contains approximately 10 grammes (12 millilitre) alcohol.

1.2 Alcohol recommendation and intake in the Netherlands

The Health Council of the Netherlands included a guideline for alcohol consumption in the *Dutch dietary guidelines 2015* (DDG-2015), which is as follows: 'Don't drink alcohol or no more than one glass daily'.[2]

In the Netherlands, people consume on average 0.9 glasses of alcoholic beverages a day.[3]

2 Methodology

2.1 Question

The committee aimed to answer the following question: What is the relationship (effect or association) of different quantities of alcohol consumption compared to no or very light alcohol consumption with health outcomes in people with ASCVD?

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*.[4]

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 the effects or associations of alcohol consumption compared to no or very light alcohol consumption. The committee aimed to compare the effects or associations of different quantities (2 or more categories on intake) of alcohol intake compared to no or very light consumption of alcohol, or continuously (per gram alcohol or per consumption of an alcoholic beverage increase). Studies in which consumers versus non-consumers of alcohol or low (including both non-consumers and people with a relatively low consumption of alcohol) versus high alcohol consumers were dichotomously compared were not taken into account in the committee's evaluation. This is because the associations of moderate and high alcohol consumption with cardiovascular health outcomes usually differ.[5] When combining the groups of moderate and high alcohol consumption, such potential differences cannot be evaluated.

In addition, the committee preferred to include studies in which alcohol 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, because people may change their alcohol consumption habits because of an ASCVD event.
The committee pooled the associations reported in all selected studies, using a random effects meta-analysis approach. The selected studies used different cut-offs for the categories of alcohol consumption, and the following approach was taken to generate estimates for comparable ranges of intakes: Per study, the intakes per reported category of alcohol consumption were translated into an average consumption of alcohol in grammes per day, similar to the approach used by Ding et al.[6] The average consumptions were then divided into the following categories of alcohol consumption (in grammes alcohol per day): 0-1 g/d (reference group); 2-15 g/d; 16-35 g/d; more than 35 g/d. This is, by approximation, similar to no or less than 1 consumption a week, 1 consumption a day, 2 to 3 consumptions a day, and more than 3 consumptions a day, respectively.
For a few of the selected studies, there were associations reported for two levels of average alcohol intake that fit within one of the categories defined by the committee. For instance, Cruijsen et al. reported associations at average intakes of 5 g/d and 14 g/d.[7] These both fit within the category of 2-15 g/d. For such studies, the lowest intake option was used in the pooled analyses, and the highest intake option was used in sensitivity analyses. In addition, one of the selected studies reported that Kaplan-Meier curves were comparable for low (on average 13 g/d) and high (on average 32 g/d) alcohol consumers compared to non-consumers, and therefore one risk estimate was presented for combined low and high consumers of alcohol.[8] This estimate was used in both the pooled analyses for the intake categories 2-15 g/d, and 16-35 g/d.
The reference group was, in the vast majority of studies, defined as current non-drinkers of alcohol. In one study it was a combination of non-drinkers and very light drinkers (i.e., 0 and 1 g/d on average), and one study used occasional consumers of alcohol (<1 drink a week) as reference group. To avoid sick-quitter bias, the committee preferred to exclude former drinkers from the reference group of non-consumers. Former drinkers may include people who have quit drinking because of sickness, making current drinkers seem healthier in comparison to less healthy non-current drinkers. There were not enough studies for an evaluation entirely based on studies excluding former drinkers in the reference group, but sensitivity analyses were performed excluding these studies.

2.4 Health outcomes

The committee selected the following health outcomes for this advisory report (further explained in the background document *Methodology for the evaluation of the evidence*[4]):

- 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, 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*.[4] In short, the committee aimed to base its evaluation of scientific literature on systematic reviews (SRs), including meta-analyses (MAs) and pooled analyses, of randomised controlled trials (RCTs) and/or prospective cohort studies examining the relationship of alcohol consumption with the above-mentioned health outcomes in people with ASCVD. To identify such publications, the committee searched PubMed and Scopus in July 2021. The search strategy and specification of the study selection 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 Selection of prospective cohort studies.

One report of an individual RCT was found. This study was described very briefly, since this single RCT gives too little evidence to base conclusions on. In addition, the committee found one MA of 15 prospective cohort studies.[6] The committee supplemented this with five individual prospective cohort studies[7-16], that were not taken into account in the MA.

2.5.2 Healthy survivor bias and sick-quitter bias

Recurring types of bias in observational studies looking into the relationship between alcohol intake and health are the healthy survivor effect and sick-quitter bias. These biases refer to alcohol consumption being a potential marker for better underlying health if only healthier drinkers survived to older age (healthy survivor bias) or if abstainers stopped drinking because of sickness (sick-quitter bias). In the evaluation of the quality of the evidence, the committee took the chances of these biases into account.

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*.[4] In short, the committee drew conclusions on (the certainty of) the evidence regarding the associations of alcohol consumption with risk of 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*[4]) as a tool to support consistency in drawing conclusions.

3 Effects and associations of alcohol consumption

In this chapter, the committee describes the scientific evidence for effects and associations of alcohol consumption with health outcomes in people with ASCVD.

3.1 RCTs

The committee found one RCT, of Marfella at al.[17] (2006), performed in 115 Italian people with diabetes and a previous MI. The participants were advised to consume the Mediterranean diet with moderate consumption of red wine (intervention group; amount of wine not reported), or the Mediterranean diet without red wine or other alcohol (control group), for 12 months. Food diaries of the control group showed no evidence of alcohol intake during the intervention period. The main outcomes of the RCT were echocardiographic parameters of functional cardiac outcome, inflammatory cytokines and nitrotyrosine. After 12 months of intervention, the concentrations of inflammatory cytokines, such as CRP and IL-6, were higher in the control group and the intervention group. In addition, myocardial performance index was higher, and transmitral Doppler flow, pulmonary venous flow analysis and ejection fraction were lower in the control group, indicating ventricular dys-synchrony. Among the secondary outcomes were systolic and diastolic blood pressure, body weight, fasting glucose and HbA1c (which were selected as surrogate outcomes for the current advisory report, and were therefore of interest to the committee). No differences in effects between the intervention and control group were found on these secondary outcomes after 12 months.
The authors reported to have no conflicts of interest. No information was provided regarding the funding of the study.

One RCT provides too little evidence to base conclusions on. Therefore, the committee concludes there is too little evidence to draw conclusions on the effects of alcohol consumption on blood pressure, body weight and HbA1c.

3.2 Cohort studies

Table 1 summarises the results and characteristics of cohort studies selected from the MA of Ding et al.[6] and complementary studies found by the committee.[7-9,15] The results of all selected studies were meta-analysed by the committee. The studies provide evidence regarding the associations of different categories of alcohol consumption with long-term health outcomes in people with ASCVD. In Annex B, the characteristics and results of the MA of Ding et al.[6] and of the complementary individual prospective cohort studies are presented in detail.

Table 1 The associations of alcohol consumption with health outcomes in people with ASCVD: meta-analyses of cohort studies

Aspect	Explanation
Number of studies	14 cohort studies in total 10 for the all-cause mortality outcome 9 for the CVD mortality outcome 6 for the total CVD outcome These cohort studies were identified from 1 MA report and 4 complementary reports of individual cohort studies[a,6-9,15]
Number of participants and cases	All-cause mortality outcome: Total number of participants: 40810 Cases: 8602 CVD mortality outcome: Total number of participants: 29299 Cases: 2262 Total CVD outcome: Total number of participants: 36776 Cases: 5658
Subtype of ASCVD (n studies)	CVD (3; 2 studies performed subgroup analyses in people with MI, angina and stroke) CHD (10) Stroke (1)
Study durations	11 studies reported the mean or median follow-up, which ranged from 1 to 13 years. 3 studies reported the maximum follow-up duration, which ranged from up to 10 to 20 years.
Dietary exposure	Alcohol consumption was self-reported. There were estimates reported for 3 or more categories of alcohol consumption. All studies assessed alcohol consumption after the occurrence of the index-ASCVD-event.
Strength of the effect	Shown in Tables 2-4
Study population	People with CVD (3 studies), CHD (10 studies) or stroke (1 study); average BMI: 24 to 29 kg/m^2; men (75 to 78%; depending on the outcome) and women (22 to 25%; depending on the outcome); medication use: NR for the majority of studies; regions: Europe, USA, Canada, Asia (Japan)

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; MA, meta-analysis; MI, myocardial infarction; NR, not reported; USA, United States of America.

Table 2 Pooled RRs (95%CI) from prospective cohort studies for the associations of different categories of alcohol consumption compared to consumption of 0-1 g/d with all-cause mortality, with I^2 indicating the extent of heterogeneity, and *n* indicating the number of studies included[d]

Analysis	2-15 g alcohol per day	16-35 g alcohol per day	>35 g alcohol per day
Main analysis	a. 0.83 (0.76, 0.91), I^2 28%, n=9 b. 0.82 (0.75, 0.90), I^2 21%, n=8 c. 0.83 (0.76, 0.90), I^2 19%, n=9	a. 0.80 (0.71, 0.90), I^2 46%, n=9 b. 0.77 (0.70, 0.85), I^2 0%, n=8	a. 0.90 (0.81, 1.01), I^2 0%, n=5
Excluding former drinkers	a. 0.87 (0.77, 0.98), I^2 35%, n=4 b. 0.85 (0.75, 0.96), I^2 32%, n=3	a. 0.92 (0.66, 1.29), I^2 79%, n=3 b. 0.79 (0.62, 1.01), I^2 54%, n=2	a. 0.96 (0.84, 1.08), I^2 0%, n=3
In males	a. 0.84 (0.77, 0.92), I^2 29%, n=6 b. 0.82 (0.74, 0.90), I^2 14%, n=5 c. 0.83 (0.76, 0.91), I^2 31%, n=6	a. 0.88 (0.66, 1.16), I^2 74%, n=5 b. 0.78 (0.62, 0.98), I^2 56%, n=4	a. 0.89 (0.77, 1.02), I^2 12%, n=4
In females	a. 0.84 (0.63, 1.10), I^2 67%, n=3 c. 0.81 (0.66, 0.99), I^2 45%, n=3	a. 0.78 (0.58, 1.05), I^2 0%, n=2	a. 0.91 (0.58, 1.41), I^2 66%, n=3
For 16-25 g alcohol per day	NA	a. 0.82 (0.65, 1.04), I^2 65%, n=5 b. 0.76 (0.65, 0.89), I^2 28%, n=4	NA
For 26-35 g alcohol per day	NA	a. 0.77 (0.67, 0.88), I^2 0%, n=4	NA

Abbreviations: CI, confidence interval; NA, not applicable; RR, relative risk.

a = Pooled result based on all available studies for this category of intake and health outcome.

b = Pooled result excluding the study by Shaper et al.[18] This study used occasional consumers of alcohol as reference group whereas the other studies included in this evaluation used non-consumers as reference group.

c = Pooled result based on all available studies, but with an RR (95%CI) for an alternative, higher category of alcohol consumption for the study by Cruijsen et al.[7] Both the lower (5 g/d on average) and higher (14 g/d on average) intake category from the study by Cruijsen et al. fit within the range of 2 to 15 g/d alcohol consumption.

[d] Alcohol intake categories of 0-1 g/d (reference group), 2-15 g/d, 16-35 g/d, and >35 g/d are equal to approximately (respectively) no or less than 1 consumption a week, 1 consumption a day, 2 to 3 consumptions a day, and more than 3 consumptions a day.

Table 3 Pooled RRs (95%CI) from prospective cohort studies for the associations of different categories of alcohol consumption compared to consumption of 0-1 g/d with CVD mortality, with I^2 indicating the extent of heterogeneity, and *n* indicating the number of studies included[d]

Analysis	2-15 g alcohol per day	16-35 g alcohol per day	>35 g alcohol per day
Main analysis	a. 0.76 (0.68, 0.86), I^2 22%, n=9 b. 0.75 (0.66, 0.85), I^2 21%, n=8 c. 0.77 (0.69, 0.87), I^2 23%, n=9	a. 0.72 (0.57, 0.90), I^2 55%, n=8 b. 0.64 (0.55, 0.76), I^2 0%, n=7	a. 0.86 (0.72, 1.03), I^2 0%, n=4
Excluding former drinkers	a. 0.77 (0.67, 0.88), I^2 0%, n=5 b. 0.74 (0.64, 0.86), I^2 0%, n=4	a. 0.74 (0.45, 1.23), I^2 76%, n=4 b. 0.65 (0.51, 0.83), I^2 33%, n=3	a. 0.84 (0.70, 1.02), I^2 0%, n=3
In males	a. 0.76 (0.67, 0.87), I^2 23%, n=6 b. 0.74 (0.64, 0.85), I^2 21%, n=5 c. 0.78 (0.67, 0.90), I^2 25%, n=6	a. 0.81 (0.59, 1.11), I^2 66%, n=5 b. 0.68 (0.56, 0.83), I^2 0%, n=4	a. 0.86 (0.70, 1.05), I^2 0%, n=4
In females	a. 0.74 (0.58, 0.95), I^2 0%, n=3 c. 0.72 (0.57, 0.92), I^2 0%, n=3	a. 0.47 (0.27, 0.82), I^2 0%, n=2	a. 0.79 (0.35, 1.81), I^2 66%, n=3
For 16-25 g alcohol per day	NA	a. 0.72 (0.47, 1.10), I^2 73%, n=5 b. 0.61 (0.49, 0.77), I^2 2%, n=4	NA
For 26-35 g alcohol per day	NA	a. 0.67 (0.54, 0.84), I^2 0%, n=3	NA

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; NA, not applicable; RR, relative risk.

a = Pooled result based on all available studies for this category of intake and health outcome.

b = Pooled result excluding the study by Shaper et al.[18] This study used occasional consumers of alcohol as reference group whereas the other studies included in this evaluation used non-consumers as reference group.

c = Pooled result based on all available studies, but with an RR (95%CI) for an alternative, higher category of alcohol consumption for the study by Cruijsen et al.[7] Both the lower (5 g/d on average) and higher (14 g/d on average) intake category from the study by Cruijsen et al. fit within the range of 2 to 15 g/d alcohol consumption.

[d] Alcohol intake categories of 0-1 g/d (reference group), 2-15 g/d, 16-35 g/d, and >35 g/d are equal to approximately (respectively) no or less than 1 consumption a week, 1 consumption a day, 2 to 3 consumptions a day, and more than 3 consumptions a day.

Table 4 Pooled RRs (95%CI) from prospective cohort studies for the associations of different categories of alcohol consumption compared to consumption of 0 g/d with total CVD, with I^2 indicating the extent of heterogeneity, and *n* indicating the number of studies included[d]

Analysis	2-15 g alcohol per day	16-35 g alcohol per day	>35 g alcohol per day
Main analysis	a. 0.80 (0.71, 0.90), I^2 9%, n=5	a. 0.87 (0.55, 1.38), I^2 77%, n=6 b. 0.96 (0.60, 1.52), I^2 79%, n=6 c. 0.75 (0.64, 0.87), I^2 47%, n=6	a. 0.76 (0.60, 0.97), I^2 59%, n=3
Excluding former drinkers	a. 0.78 (0.69, 0.87), I^2 6%, n=3	a. 1.16 (0.48, 2.84), I^2 84%, n=3 c. 0.70 (0.62, 0.80), I^2 0%, n=3	a. 0.71 (0.58, 0.86), I^2 NA, n=1
In males	a. 0.71 (0.60, 0.83), I^2 0%, n=3	a. 1.04 (0.36, 2.99), I^2 87%, n=3 c. 0.65 (0.55, 0.77), I^2 32%, n=3	a. 0.70 (0.56, 0.88), I^2 NA, n=1
In females	a. 0.78 (0.63, 0.97), I^2 NA, n=1	a. 0.84 (0.64, 1.10), I^2 NA, n=1	a. 0.61 (0.38, 0.99), I^2 NA, n=1
For 16-25 g alcohol per day	NA	a. 0.74 (0.59, 0.93), I^2 49%, n=4	NA
For 26-35 g alcohol per day	NA	a. 1.16 (0.62, 2.17), I^2 82%, n=4 c. 0.79 (0.65, 0.96), I^2 44%, n=4	NA

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; NA, not applicable; RR, relative risk.

a = Pooled result based on all available studies for this category of intake and health outcome.

b = Pooled result based on all available studies, but with RRs (95%CI) based on alternative, higher categories of alcohol consumption for the studies of Bryson et al.[9] and Mukamal et al.[15] Both the lower (20 and 18 g/d on average, respectively) and higher (34 and 28 g/d on average, respectively) intake categories from these studies fit within the range of 16 to 35 g/d alcohol consumption.

c= Pooled result excluding the subgroup analyses from the study by Masunaga et al.[19] focused on people aged ≥ 65 years. The study by Masunaga et al. performed analyses for people aged <65 years and ≥65 years separately.

[d] Alcohol intake categories used in the analyses were 0 g/d (reference group), 2-15 g/d, 16-35 g/d, and >35 g/d. These intakes are equal to approximately (respectively) non-consumption, 1 consumption a day, 2 to 3 consumptions a day, and more than 3 consumptions a day.

Table 5 Associations of alcohol consumption compared to 0-1 g of alcohol consumption per day with health outcomes in people with stroke, results from individual cohort studies

Outcome	Author/ Study name	2-15 g alcohol / day[c] n participants; n cases; HR (95%CI)	16-35 g alcohol / day[c] n participants; n cases; HR (95%CI)	>35 g alcohol / day[c] n participants; n cases; HR (95%CI)
All-cause mortality	Jackson et al.[20]	417; 93; 0.64 (0.48, 0.85)	409; 109; 0.71 (0.54, 0.94)	NA
All-cause mortality	HSE/HSeSs[6]	286; 145; 1.22 (0.73, 2.07)	97; 50; 1.26 (0.69, 2.30)[a]	97; 50; 1.26 (0.69, 2.30)[a]
All-cause mortality	UK Biobank[6]	866; 80; 0.46 (0.30, 0.71)	699; 93; 0.54 (0.35, 0.85)	133; 22; 0.74 (0.41, 1.32)
CVD mortality	Jackson et al.[20]	417; 62; 0.56 (0.40, 0.79)	409; 75; 0.64 (0.46, 0.88)	NA
CVD mortality	HSE/HSeSs[6]	286; 56; 1.49 (0.65, 3.45)	87; 15; 1.40 (0.52, 3.75)	10; 4; 2.84 (0.70, 11.51)
CVD mortality	UK Biobank[6]	865; 29; 0.50 (0.23, 1.08)	699; 26; 0.45 (0.20, 1.01)	133; 10; 1.03 (0.40, 2.65)
Total CVD[b]	UK Biobank[6]	866; 107; 0.61 (0.40, 0.92)	699; 90; 0.57 (0.36, 0.88)	133; 13; 0.47 (0.24, 0.91)

Abbreviations: CVD, cardiovascular disease; HSE/HSeSs, Health Survey for England / Scottish Health Survey; UK, United Kingdom.

[a] Combined consumers of 16-35 g/d and >35 g/d;

[b] For this outcome, non-consumers of alcohol are the reference group (thus 0 g/d of alcohol);

[c] Alcohol intake categories of 0-1 g/d (reference group), 2-15 g/d, 16-35 g/d, and >35 g/d are equal to approximately (respectively) no or less than 1 consumption a week, 1 consumption a day, 2 to 3 consumptions a day, and more than 3 consumptions a day.

Conclusions:

Prospective cohort studies show that people with ASCVD who consume 2 to 35 grammes of alcohol per day, compared to people who consume 0 to 1 grammes of alcohol per day have an approximately 20% lower risk of all-cause mortality. The evidence is strong. At higher intakes, there is likely no association compared to consumption of 0-1 grammes of alcohol per day.

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 10 cohort studies that address the association between various levels of alcohol consumption and all-cause mortality, with a total >500 events.[6-8,18,20-24] This is the first step required to mark the evidence as strong (for which at least 5 studies and 500 cases are needed).

2. Heterogeneity of the study findings:
   A pooled analysis of these cohort studies showed statistically significant reductions in the risk of all-cause mortality with intakes of 2 to 15 (based on 9 studies) and 16 to 35 (based on 9 studies) grammes of alcohol per day compared to intakes of 0 to 1 grammes of alcohol per day. The pooled estimates are presented in Table 2.
   For intakes between 2 to 15 g/d of alcohol, there was little heterogeneity between studies. For intakes of 16 to 35 g/d, there was moderate heterogeneity (46%) in the main pooled result. Excluding the study by Shaper et al.[18] slightly strengthened the association, and reduced heterogeneity (I^2 0%). That study used occasional consumers of alcohol (average intake 1 gram per day) as reference group whereas the other studies used non-consumers as reference group. This may explain the difference in results with the other studies. Estimates for intakes of 2 to 15 and 16 to 35 g/d alcohol were not substantially different, and the confidence intervals overlapped to a large extent. The data do not allow the identification of an optimal intake of alcohol within this range of 2 to 35 g/d.
   For intakes higher than 35 g/d of alcohol compared to 0-1 g/d, only 5 out of the 10 cohort studies contributed data to the estimates. The pooled result of these studies showed there was likely no association with risk of all-cause mortality, without heterogeneity between studies.

3. Considerations regarding the quality of the evidence:
   The committee selected studies for its evaluation in which alcohol intake was assessed after the occurrence of the index-event. It cannot be excluded that some of the studies measured alcohol consumption in the acute phase of the disease (within 6 months after diagnosis), and may be less representative of the post-event, long-term, habitual intake.
   All but one study used non-consumers of alcohol as reference group. Moreover, a large number of these studies included former drinkers in the reference group of non-drinkers, which may have induced sick-quitter bias. Sensitivity analyses excluding studies with former drinkers in the reference group showed that results attenuated slightly but were not substantially different from the main result, in particular taking into account that these analyses were based on relatively few studies (up to 4 studies). The committee additionally notes that, from studies in the general population, it is known that non-drinkers (both former drinkers and abstainers) generally have a higher risk of mortality than consumers of alcohol. In line with this, the committee found heterogeneity in results caused by one study that used occasional drinkers as reference group instead of non-drinkers. However, the committee is not able to draw conclusions on the associations of alcohol consumption and mortality specifically in alcohol consumers only because the design of the vast majority of included studies in people with ASCVD did not allow

for such an evaluation.
In general, the studies adjusted for relevant confounders, and at least age, sex and smoking. Except one study[8], that did not adjust for smoking status. Moreover, some of the studies did not adjust for the use of cholesterol- and blood pressure lowering medication, and most studies did not adjust for dietary factors, including energy intake. Given there is no to little heterogeneity between studies (after excluding the study by Shaper et al.), such differences between studies likely did not substantially impact the results.

4. Generalisability:
   The majority of participants in the evaluated studies were men (~32000 [78%] men and ~9000 [22%] women). Nevertheless, the observed pooled associations were very similar for men and women and not substantially different from the main results, though with high levels of heterogeneity for women (at intakes of 2-15 and >35 g/d) and men (at intakes of 16-36 g/d). Also, the associations generally did not reach statistical significance in women. This may be a consequence of the (relatively) small number of studies that provided results specifically for men (4 to 6; depending on the alcohol intake category) and women (2 to 3), and that some of the subgroups were rather small. Such subgroup analyses increase the likelihood of obtaining instable results and chance findings. Based on the current observations, the committee concludes there is more uncertainty about the associations in women than in men, but the committee sees no reason to expect the associations would be substantially different for men and women.

Prospective cohort studies show that people with ASCVD who consume 2 to 35 grammes of alcohol per day, compared to people who consume 0 to 1 grammes of alcohol per day have an approximately 25 to 35% lower risk of cardiovascular mortality. The evidence is strong. There are too few studies to draw a conclusion on the associations of higher intakes of alcohol with the risk of cardiovascular 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 9 cohort studies that address the association between various levels of alcohol consumption and CVD mortality, with a total >500 events.[6,7,18,20-23,25] This is the first step required to mark the evidence as strong (for which at least 5 studies and 500 cases are needed).

2. Heterogeneity of the study findings:
   A pooled analysis of these 9 cohort studies showed a statistically significant reduction in the risk of CVD mortality with intakes of 2 to 15 (based on 9 studies) and 16 to 35 (based on 8 studies) grammes of alcohol per day compared to intakes of 0 to 1 grammes of alcohol per day. The pooled estimates are presented in Table 3.
   For intakes between 2 to 15 g/d of alcohol, there was little heterogeneity between studies. For intakes of 16 to 35 g/d, there was a high level of heterogeneity (55%) in the main pooled result. Excluding the study by Shaper et al.[18] slightly strengthened the association, and reduced heterogeneity (I^2 0%). That study used occasional consumers of alcohol (average intake 1 gram per day) as reference group whereas the other studies used non-consumers as reference group. This may explain the difference in results with the other studies.
   Estimates for intakes of 2 to 15 and 16 to 35 g/d alcohol were not substantially different, and the confidence intervals overlapped to a large extent. The data do not allow the identification of an optimal intake of alcohol within this range of 2 to 35 g/d.
   For intakes higher than 35 g/d of alcohol compared to 0-1 g/d, only 4 out of the 9 cohort studies contributed data to the estimates. The pooled result of these studies showed a tendency towards a reduction in risk of approximately 15%, but this was not statistically significant. There was no heterogeneity between studies. The small number of studies limited the committee in concluding on whether there was an inverse or no association.

3. Considerations regarding the quality of the evidence:
   The committee selected studies for its evaluation in which alcohol intake was assessed after the occurrence of the index-event. It cannot be excluded that some of the studies measured alcohol consumption in the acute phase of the disease (within 6 months after diagnosis), and may be less representative of the post-event, long-term, habitual intake.
   All but one study used non-consumers of alcohol as reference group. Moreover, a large number of these studies included former drinkers in the reference group of non-drinkers, which may have induced sick-quitter bias. Sensitivity analyses excluding studies with former drinkers in the reference group showed rather similar results. The committee also notes that, from studies in the general population, it is known that non-drinkers (both former drinkers and abstainers) generally have a higher risk of mortality than consumers of alcohol. In line with this, the committee found heterogeneity in results caused by one study (Shaper et al.) that used occasional drinkers as reference group instead of non-drinkers. However, the committee is not able to draw conclusions on the associations of alcohol consumption and CVD mortality specifically in alcohol consumers only because the

design of the vast majority of included studies in people with ASCVD did not allow for such an evaluation.
In general, the studies adjusted for relevant confounders, and at least age, sex and smoking. Some of the studies did not adjust for the use of cholesterol- and blood pressure lowering medication, and most studies did not adjust for dietary factors, including energy intake. Given there is no to little heterogeneity between studies (after excluding the study by Shaper et al.), such differences between studies likely did not substantially impact the results.

4. Generalisability:
   The majority of participants in the evaluated studies were men (~22000 [77%] men and ~7500 [23%] women). Nevertheless, the observed pooled associations at intakes of 2 to 15 and 16 to 35 g/d were rather comparable for men and women and not substantially different from the main results, in particular taking into account that for some of these subgroup analyses relatively few studies could be taken into account (for men 4 to 6, and for women 2 to 3 studies, depending on the alcohol intake category). Based on the current observations, the committee concludes there is more uncertainty about the associations in women than in men, but the committee sees no reason to expect the associations would be substantially different for men and women.

Prospective cohort studies show that people with ASCVD who consume 2 to 35 grammes of alcohol per day, compared to people who abstain from alcohol have an approximately 20% lower risk of total cardiovascular disease. The evidence is strong. There are too few studies to draw a conclusion on the associations of higher intakes of alcohol with the risk of total cardiovascular disease 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 6 cohort studies that address the association between various levels of alcohol consumption and total CVD (cardiovascular morbidity and mortality), with a total of >500 cases, that address this topic.[6,9,15,19,24,26] This is the first step required to mark the evidence as strong (for which at least 5 studies and 500 cases are needed).

2. Heterogeneity of the study findings:
   For intakes between 2 and15 g/d of alcohol compared to no intake of alcohol, there was little heterogeneity (I^2 9%) in results between studies. The pooled estimates

are presented in Table 4.
For intakes of 16 to 35 g/d, there was a high level of heterogeneity (I^2 77%) in the main pooled result. The study by Masunaga et al.[19] showed, in contrast to the other studies (that showed reductions in risks of CVD events), an increased risk for CVD events in people aged ≥ 65 years and no association in people aged <65 years. Excluding the study in people aged ≥ 65 years reduced heterogeneity but there remained moderate heterogeneity, likely explained by the study in people aged <65 years. The committee noted methodological concerns regarding the study by Masunaga et al., and therefore based its conclusions on the estimates discarding this study. In particular, the committee noted the relatively short follow-up of 1 year. Due to this, the presented associations less likely are a good reflection of the association between habitual, long-term intake of alcohol and risk of CVD events. In addition, the small number of CVD cases (likely due to the short follow-up), in particular in the group of people aged ≥ 65 years, likely made the results more sensitive to outliers. Differences in characteristics of study participants and definitions of outcomes between studies may have contributed to heterogeneity as well.
Estimates for intakes of 2 to 15 and 16 to 35 g/d alcohol compared to no consumption of alcohol were not substantially different, and the confidence intervals overlapped to a large extent. The data do not allow the identification of an optimal intake of alcohol within this range of 2 to 35 g/d.
For intakes higher than 35 g/d of alcohol compared to no consumption of alcohol, only 3 out of the 6 cohort studies contributed data to the estimates. The pooled result of these studies showed a reduction in the risk, but there was substantial heterogeneity between studies (I^2 59%), with one study showing no association and the other two showing reductions in risks. The small number of studies and heterogeneity between these studies limited the committee in concluding on the association between alcohol consumption higher than 35 g/d and total CVD.

3. Considerations regarding the quality of the evidence:
   The committee selected studies for her evaluation in which alcohol intake was assessed after the occurrence of the index-event. It cannot be excluded that some of the studies measured alcohol consumption in the acute phase of the disease (within 6 months after diagnosis), and may be less representative of the post-event, long-term, habitual intake.
   All studies used non-consumers of alcohol as reference group. Moreover, several of these studies included former drinkers in the reference group of non-drinkers, which may have induced sick-quitter bias. Sensitivity analyses excluding studies with former drinkers in the reference group showed rather similar results (after excluding the study by Masunaga et al.). The committee also notes that, from studies in the general population, it is known that non-drinkers (both former drinkers

and abstainers) generally have a higher risk of CVD than consumers of alcohol. However, the committee is not able to draw conclusions on the associations of alcohol consumption and CVD mortality specifically in alcohol consumers only because the design of the included studies in people with ASCVD did not allow for such an evaluation.
In general, the studies adjusted for relevant confounders, and at least age, sex and smoking. Some of the studies did not adjust for the use of cholesterol- and blood pressure lowering medication, and most studies did not adjust for dietary factors, including energy intake. Given there is no substantial heterogeneity between studies (after discarding the study by Masunaga et al.), such differences between studies likely did not substantially impact the results.

4. Generalisability:
   The majority of participants in the evaluated studies were men (~28000 [75%] men and ~9000 [25%] women). There was only one study with estimates for women specifically, and 1 to 3 studies (depending on the category of intake) with estimates in men specifically, which is too little to draw conclusions for men and women separately. However, the observed (pooled) associations in men and women were not substantially different from each other and from the overall results. Based on this observation, the committee concludes there is more uncertainty about the associations in women than in men, but the committee sees no reason to expect the associations would be substantially different for men and women.

There are too few studies to draw a conclusion on the association between alcohol consumption and congestive heart failure in people with ASCVD.

There is only one individual cohort study that addresses this topic[9], which provides too little evidence to base conclusions on.

Regarding subtypes of ASCVD:
The committee sees no indications that the observed associations would be substantially different in people with CHD or stroke. Studies performed specifically in people with PAD were not found.
The evidence that contributed to the above given conclusions is largely driven by studies performed in people with CHD. Moreover, the majority of cases in the current analyses are expected to be cases of CHD. Results of studies performed in (subgroups of) people with stroke are shown in Table 5. There were too few studies and cases to draw separate conclusions for people with stroke. However, the largest studies performed in people with stroke showed that the results were, by approximation, in line with the overall results (slightly stronger associations). Based on these observations, the committee sees no reason to expect differences in associations between people

with CHD or stroke on all-cause mortality, CVD mortality and total CVD outcomes. However, people with stroke may be particularly at risk of developing a subsequent stroke. In the general population, relatively higher compared to lower consumption of alcohol consumption has been associated with increased risk of stroke in consumers of alcohol.[5,27] Estimates for associations with risk of stroke in people with stroke or another type of ASCVD were not available for the committee's evaluation. Therefore, it is, from the current evaluation, uncertain whether the evaluated alcohol intakes also associate with risk of stroke.

The committee sees no reason to draw separate conclusions for specific subgroups of ASCVD (namely CHD, stroke, PAD), except for the 'graft progression' outcome, which is only applicable to people with CHD who previously underwent a CABG. The conclusion for this subgroup is as follows: There are too few studies (n=1[15]) to draw a conclusion on the association between alcohol consumption and graft progression in people with CHD who previously underwent CABG.

Explanation regarding the pooled analyses of studies performed by the committee:

The committee found one MA, of Ding et al.[6] that reported on 15 cohort studies on the association between alcohol consumption and health outcomes in people with ASCVD. Of these, 11 measured the alcohol consumption after the index event. These were selected for the committee's evaluation. For practical reasons, the committee counted the HSE/HSeSs cohorts as one cohort instead of 2 (as was done by Ding et al.) since only one combined risk estimate was given for these cohorts by Ding et al. Therefore, the committee counts 10 studies selected from the MA of Ding et al. In addition, 4 complementary individual cohort studies were found by the committee.[7-9,15] The evidence obtained from these studies is described in brief below. The studies are summarised in Table 1 and Annex B, and the pooled estimates are shown in Tables 2 to 4.

The pooled analyses showed that intakes of 2 to 35 g of alcohol per day, compared to no intake or up to 1 gram per day, associates with reductions in the risks of all-cause mortality and CVD mortality. At intakes of 2 to 15 g/d, there was little heterogeneity between studies (I^2 22% and 28%, respectively). At intakes of 16 to 35 g/d, there was substantial heterogeneity (I^2 46% and 55%, respectively). This was explained by the study by Shaper et al.[18] Excluding that study generally (slightly) strengthened the inverse associations, and substantially reduced the extent of heterogeneity. Shaper et al. reported increased risks of all-cause and CVD mortality with alcohol consumption of on average 25 g/d whereas the other studies reported (tendencies towards) reductions in risks at such intakes. The study by Shaper et al. involved 596 men from the United Kingdom with a previous MI or angina. After a mean follow-up of 12.8 years, 258 and

184 cases of, respectively all-cause and CVD mortality occurred. Shaper et al. used occasional drinkers as reference group (defined as <1 drink a week), whereas the other studies used non-drinkers as reference group. This may explain the differences in results with other studies. Ex-drinkers had higher risks for all-cause and CVD mortality compared to occasional drinkers, but never drinkers had comparable risks to occasional drinkers in the study by Shaper et al. Therefore, it cannot be excluded there may also be other, unexplained reasons for the heterogeneity. On the other hand, the group of never drinkers was rather small. This may have hindered Shaper et al. to detect a difference between these groups. Indeed, the confidence intervals were rather wide for the comparison of never drinkers with occasional drinkers. Therefore, the committee deems it likely that the use of the occasional drinkers as reference group caused the heterogeneous findings.

For the total CVD outcome, the pooled analyses showed that intakes of 2 to 35 g of alcohol per day, compared to no intake or up to 1 g per day, associates with reductions in risks. At intakes of 2 to 15 g/d, there was little heterogeneity between studies. At intakes of 16 to 35 g/d, there was substantial heterogeneity. This was to a large extent explained by the study by Masunaga et al.[19] That study included 3845 men with a previous MI, from Japan. During a mean follow-up of 1 year, 142 CVD events occurred. Former drinkers were excluded from the reference group of non-drinkers. Masunaga et al. presented results for men aged below 65 years and aged 65 years and older separately. The subgroup of men aged 65 years and older was relatively small (n=844). In the men aged 65 years and older, an increased risk was found of 5.75 (95%CI: 2.21, 14.90). In the younger men, no statistically significant association was found (0.92 (95%CI: 0.51, 1.66)). Both findings, but particularly the finding in the men aged 65 years and older, were not in line with the results of other studies included in the evaluation. These all reported (tendencies) towards reductions in the risks of CVD events. This included the study by Bryson et al.[9], which specifically included people of 65 years and older. The committee expects the short follow-up and relatively small number of cases that occurred, may have contributed to the heterogeneous findings. Due to the short follow-up, the associations are less likely a good reflection of the association between the habitual, long-term intake of alcohol with CVD risk. Also, the results were likely more sensitive for outliers due to the small number of cases that occurred. Perhaps, also differences in cultural background have played a role since this was the only study included that was performed in Asian people.
Furthermore, the definition of CVD events differed between studies. For instance, for the study by Bryson et al. it included incident (fatal and non-fatal) congestive heart failure and cardiovascular death. For Masunaga et al. it included cardiac events (fatal and non-fatal MI, death from heart failure, and sudden death) or stroke. This may also, to some extent, have contributed to heterogeneity.

General limitations of the studies included in the committees evaluation are that alcohol consumption was self-reported (mostly via questionnaires) by the participants, which may have led to an underestimation of alcohol intake, in particular at higher alcohol intakes.[28] The assessment of alcohol consumption with dietary questionnaires such as food frequency questionnaires (FFQ's) was done in only a minority of studies. In general, FFQ's are known to have a relatively high validity for alcohol intake assessment.[29] However, in most studies, alcohol was assessed as part of general (health-related) questionnaires or was obtained from a clinical database. The validity of such alcohol assessments was not reported. Furthermore, changes in drinking behaviour were generally not captured, and drinking patterns, including binge drinking, and consumption of different types of alcohol were not taken into account.

Summaries of the MA of Ding et al. and individual cohort studies selected by the committee

Below, the MA of Ding et al.[6] (results for the 10 studies that were selected for the committees evaluation) and 4 individual studies[7-9,15] that contributed to the committees evaluation are described. The characteristics and results of these studies are summarised in Annex B.

From the MA report of Ding et al.[6] (2021) the committee selected 10 cohort studies (counting the HSE/HSeSs as 1 cohort) that assessed alcohol consumption after the index- event. The studies together involved between 21,525 and 37,245 participants with a previous MI, angina, or stroke prior to baseline and 2003 to 6546 cases (depending on the outcome).

Outcomes were all-cause mortality, cardiovascular mortality, and major cardiovascular events. Most of the studies were prospective cohort studies, and some had an RCT design by origin (for certain drug or diet types with no specific interventions on alcohol consumption). Alcohol consumption was self-reported, and mostly once at baseline. It was not reported how long after the event the alcohol consumption was assessed.

Ding et al. performed a dose-response meta-analysis based on studies that reported on at least 3 drinking categories, including a non-drinking group. The alcohol consumption per category was converted into grammes per day, based on the reported average consumption per drinking category. When averages were not reported, the midpoints were chosen. For open-ended upper categories, mean values were defined as 1.2 times the lower boundary (based on the article of Berlin et al.[30]). Sensitivity analyses multiplying the lower boundary by 1.0, 1.4 or 1.6 showed similar results. When the number of drinks was reported, this was converted into grammes per day based the reported quantities in the paper or based on country specific standards. Exposures categorised according to time periods longer than one day were transferred into daily estimates, assuming an even distribution of consumption over the reference period.

All but one study used a non-drinking reference group. This group was used as reference group. For one study that used occasional drinkers as reference group, the risk estimates were recalculated to derive estimates relative to a non-drinking group using a spreadsheet developed by Hamling et al.[31]
For each study, the best fitting second-degree fractional polynomial family model was identified for the exposure variable. A two-stage regression model was fitted to summarise the relationship of alcohol with the outcome of interest. The first stage generated a dose-response model within each study, and the second model pooled the study-specific trends, using a random-effects model.
Based on this approach, Ding et al. reported J-shaped associations, with maximum effect sizes (RR) of 0.81 (95%CI: 0.74, 0.88) for all-cause mortality, 0.73 (95%CI: 0.60, 0.90) for CVD mortality and 0.50 (95%CI: 0.26, 0.96) for CVD events. These were found for intakes of 9, 8 and 6 g/d compared to abstention of alcohol, respectively. For CVD events, there was a high amount of heterogeneity (I^2 75%). Reversion points were also reported (points at which the associations are no longer statistically significantly protective), and ranged from 3 to 52 g/d. There were relatively few data-points for relatively higher intakes of alcohol. This likely contributed to uncertainty in the reported reversion points. Several other (sensitivity) analyses were performed, such as analyses for men and women separately and analyses excluding studies with former drinkers in the reference group of non-consumers of alcohol. The results of these analyses are presented in Annex B. It should be noted that these analyses were based on all available studies included by Ding et al., and thus not per se on the committee's selection of studies that measured alcohol consumption after the occurrence of the index-event.
Overall, the quality of the included studies was judged moderate to high by Ding et al., with a median score of 8 on the Newcastle-Ottawa Scale. Sensitivity analyses excluding studies with the lowest quality (score <7) resulted in similar results.
The reported associations were adjusted for relevant confounders, at least age, sex and smoking. Some studies did not adjust for the use of cholesterol-lowering and/or blood pressure lowering medication. The majority of studies included in the MA did not adjust for dietary factors, including energy intake.
There were no notable funding sources or conflicts of interest reported in the MA report.

In order to combine effect estimates of the studies included by Ding et al. with these of other studies selected by the committee, the RRs per category of intake of alcohol consumption, per study, were combined using a random effects meta-analysis approach (thus not the RRs for maximum effect sizes calculated by Ding et al). The pooled results presented by of Ding et al. are in line with the findings of the committee.

The study by Bryson et al.[9] (2006) showed that moderate drinking relative to abstention was associated with a lower risk of congestive heart failure (CHF) in people with CVD. The association tended to be stronger for people who drank 7 to 13 drinks a week than for those who drank 1 to 6 drinks per week. There was no association between the consumption of more than 14 drinks per week and the risk of CHF relative to abstainers. For the CHF and cardiovascular mortality outcomes, results with respect to moderate alcohol consumption compared to abstaining alcohol consumption were very comparable to the results for the incident CHF outcome alone. A strength of this study is that former drinkers were differentiated from abstainers, and that abstainers were used as reference group, thereby reducing the chance of sick-quitter bias. Former drinkers had a higher risk of CHF than abstainers but quitting during the study was not associated with the risk of CHF (HR 0.83, CI 0.66, 1.03). Alcohol consumption was assessed after the occurrence of the index event, but it was unknown how long after the index-event this took place. A sensitivity analysis involving lagged analyses was performed to examine the association between baseline alcohol consumption and events occurring after an imposed delay of 1 to 5 years. This did not alter the results, and suggests the results apply to the non-acute phase after the CVD event. The study had a relatively high number of participants and cases and included roughly a similar share of men and women.

In the main analyses of the study by Cruijsen et al.[7] (2021), former drinkers were included in the reference group of non-drinkers and very light drinkers (up to 2 g alcohol a day). The committee selected sensitivity analyses for its evaluation in which former drinkers were excluded from this reference group. In these analyses, light and moderate alcohol drinking was inversely associated with the risk of cardiovascular mortality, and ischemic heart disease mortality, relative to non-drinking or very light drinking in people who had experienced an MI. There was no statistically significant association with all-cause mortality. Heavy drinking and binge drinking were not statistically significantly associated with the risk of these outcomes. For the full cohort (thus including former drinkers in the reference group), the results were not very different when only very light drinkers or only abstainers were used as reference group. This suggests sick-quitter bias or other abstainer related bias (e.g., alcohol use deniers: heavy drinkers misclassified in the non-drinking group) did not seem to play a major role.
In subgroup analyses (based on the full cohort) by sex, the associations were rather similar to the overall analyses for men, and there were no statistically significant associations in women, possibly due to the relatively low number of women included in the study.
To establish potential thresholds or non-linear associations, restricted cubic spline analyses were used. These analyses were performed in the full cohort. In these analyses, alcohol intake was non-linearly significantly inversely associated with all-

cause, cardiovascular, and ischemic heart disease mortality in men, with the lowest risk observed at 20 g/d. In women, the associations for light and moderate alcohol intake were also inverse, with the lowest risk around 10 g/d, but not statistically significant. Again, this is possibly due to the relatively small number of women included in the study.
Alcohol consumption was assessed at baseline, after the occurrence of the index-event (MI) but it was not reported how long after the event. The observed associations (in the full study cohort) did not substantially change when participants that experienced an MI less than one year before enrolment were excluded, indicating that the results are representative for the habitual alcohol consumption, beyond the acute phase.
The study had a relatively high number of participants and cases, and long follow-up. Adjustments for relevant confounders were made, such as for smoking, physical activity, energy intake and intake of foods including sugar sweetened beverages, red and processed meat and fish. Participants were predominantly male (79%), therefore limiting the generalisability of the results to women.

In the study by Iestra et al.[8] (2006), the risk of all-cause mortality in alcohol consumers versus abstainers was assessed in people who had experienced an MI. Kaplan-Meier survival curves did not show a difference between the curves of moderate drinkers and excessive drinkers. For this reason, these two groups were compared in the analysis: consumers and abstainers of alcohol. Alcohol consumption was associated with a lower risk of all-cause mortality relative to abstention. However, this association was not statistically significant. This may be due to the small number of participants and cases in the study. Two in three participants was male, and there were no differences in the associations between men and women. When looking at the association for Northern and Southern European countries separately, there was a reduction in the risk in Northern Europeans for alcohol consumption compared to abstention (HR 0.62, CI 0.44, 0.89), whereas there was no association for Southern Europeans (HR 1.01 CI 0.58, 1.76). There was no explanation given by the authors for these differences in findings. It should be noted that no adjustments were made for smoking, physical activity, energy intake and dietary factors in these particular analyses, while this information was available. No reasons were provided for this by the authors. Moreover, it was not mentioned whether former drinkers were excluded from the abstainers group and therefore the possibility of sick-quitter bias influencing the results cannot be excluded. Alcohol consumption was measured at baseline. It was not reported how long after the MI event the alcohol consumption was assessed. However, given the participants were a selection from general (elderly) population cohorts, the committee expects the alcohol consumption was assessed outside the acute phase of the MI event.

The study by Mukamal et al.[15] (2006) showed that moderate alcohol consumption was associated with a lower risk of angiographic graft worsening and clinical events, relative to abstention in people who had underwent a CABG. However, these associations were not statistically significant. This may be due to the relatively small number of cases. Former drinkers were likely part of the group of abstainers, and therefore the possibility of sick-quitter bias influencing the results cannot be excluded. A sensitivity analysis was performed in which the abstainers with a reported or suspected history of previous excessive alcohol use were excluded. The results were unchanged, thereby partly limiting the possibility of sick-quitter bias. Another sensitivity analysis was performed by restricting the endpoint in the analysis to death or non-fatal MI, and thus eliminating revascularization endpoints. The authors reported that identical relative risks were obtained for death and non-fatal MI, but with wider confidence intervals. However, the numerical results were not presented. In addition, analyses with cubic splines were performed to assess the dose response relationship between alcohol consumption and the risk of clinical events and the risk of angiographic progression. The risk for clinical events was lowest in consumers of 6 to 8 drinks per week and exceeded abstainers at 11 to 13 drinks per week. For angiographic progression, the risk was lowest for consumers of 10 to 11 drinks per week and remained significant up to 16 to 19 drinks per week.
Alcohol consumption was assessed at baseline. Since the baseline was at least one year after the CABG procedure, the committee concludes the alcohol intake was assessed outside the acute phase and therefore likely reflects the habitual post-event intake. Adjustments were made for relevant potential confounders such as smoking, physical activity, intakes of energy, protein and fat. This study was performed predominantly in male (92%), therefore limiting the applicability of the results to women.

For all the above-described individual studies, there were no notable funding sources or conflicts of interest reported that might have influenced the results of the studies.

3.3 Summary of conclusions

The committee's conclusions regarding effects and associations of alcohol consumption with health outcomes in people with ASCVD are summarised in Table 6.

Table 6 Overview of conclusions regarding the effects and associations of alcohol consumption with health outcomes in people with ASCVD

Level of alcohol intake	Health outcome[a]	Study design	Conclusion
Moderate (not further defined) versus 0 g/d	Blood pressure, body weight, HbA1c	RCTs	Too little research
2-35 g/d versus 0-1 g/d	All-cause mortality	Cohort studies	20% reduced risk; strong evidence
>35 g/d versus 0-1 g/d	All-cause mortality	Cohort studies	No association
2-35 g/d versus 0-1 g/d	CVD mortality	Cohort studies	25-35% reduced risk; strong evidence
>35 g/d versus 0-1 g/d	CVD mortality	Cohort studies	Too little research
2-35 g/d versus 0 g/d	CVD events	Cohort studies	20% reduced risk; strong evidence
>35 g/d versus 0 g/d	CVD events	Cohort studies	Too little research

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; HbA1c, Glycated haemoglobin; RCTs, randomised controlled trials.

[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.

On the topic of moderate alcohol consumption and CVD risk, both an RCT and cohort studies were available. Cohort studies showed that moderate (2-35 g/d) alcohol consumption associated with a reduction in the risk of CVD morbidity and mortality. In contrast, the RCT found no effect of moderate wine consumption on blood pressure[17], which is defined as a surrogate outcome for CVD by the committee. Blood pressure was a secondary outcome, and the study may have been underpowered for finding an effect on blood pressure. One RCT provides too little evidence to base separate RCT-based conclusions on, and this limits the comparison of evidence from cohort studies with the evidence from the RCTs.

3.4 Comparison with findings in the general population

The committee compared the conclusions for people with ASCVD with the conclusions drawn for the general population in the DDG-2015.[2,27] Moreover, the conclusions were additionally compared to findings from a more recent report of Wood et al. (2018) on the association between alcohol consumption and health outcomes in a large sample of the general population.[5] Based on these comparisons, the committee concludes the findings in people with ASCVD, regarding the all-cause mortality, CVD morbidity and CVD mortality outcomes, are very much in line with these from the general population.

3.4.1 Comparison with *Dutch dietary guidelines 2015*

In the DDG-2015, the guideline on alcohol consumption is as follows: ‘Don’t drink alcohol or no more than one glass daily’.[2] This is based on the conclusions regarding evidence from cohort studies and RCTs listed in the text box below. In addition, this

guideline was based on the evidence for alcoholic beverages such as beer and liquor, for which, among other things, associations with multiple types of cancer were found.[32]

DDG-2015 conclusions on alcohol with a strong level of evidence[27]
RCTs:

- Systolic blood pressure:
  1.0 mmHg reduction per 10% reduction of alcohol intake.

Cohort studies:

- All-cause mortality:
  Lowest mortality risk at 6 g/day. With this level of intake, there is a 15% reduced risk of mortality compared to no alcohol consumption.
- Coronary heart disease:
  (1) 25% reduced risk with average consumption of at least 2.5 g/d compared to no alcohol consumption;
  (2) Binge drinking is associated with a 45% higher risk compared to evenly spread alcohol consumption, at equal amounts of intake.
- Stroke:
  (1) 20% increased risk with alcohol consumption of > 0 to 15 g/d compared to no alcohol consumption;
  (2) 35% increased risk with alcohol consumption of ≥ 30 g/d compared to > 0 to 15 g/d.
- Heart failure:
  20% reduced risk with alcohol consumption of 2 to 28 g/d compared to 0 g/d.
- Type 2 diabetes:
  20% reduced risk with alcohol consumption of 0 to 24 g/d in men and 6 to 48 g/d in women.
- Colon cancer:
  20% increased risk with alcohol consumption of 30 to 60 g/d compared to 0 g/d.
- Breast cancer, in women:
  (1) 5% increased risk with alcohol consumption of 5 to 15 g/d compared to 0.1 to 5 g/d;
  (2) 10% increased risk with alcohol consumption of 15 to 30 g/d compared to 0.1 to 5 g/d.
- Dementia:
  25% reduced risk with alcohol consumption of >0 to 30 g/d compared to no alcohol.

For the current advisory report, focused on people with ASCVD, the committee could only evaluate studies that focused on CVD outcomes and all-cause mortality. Regarding CVD outcomes, there were reductions in the risks of approximately 20-35% (depending on the outcome) for intakes of alcohol between 2-35 g/d compared to 0-1 g/d in people with ASCVD. The DDG-2015 conclusions on CVD outcomes (coronary artery disease, stroke, heart failure) were of risk reductions of approximately 20% for intakes between 0 and 15 or 28 g (depending on the outcome) alcohol per day or from at least 2.5 g/d (for coronary heart disease). This latter association was statistically significant up to the category of alcohol intake of 30-60 g/d. The findings in people with ASCVD are not very different from these reported in the DDG-2015. The associations tend to be slightly stronger in people with ASCVD. In both people with ASCVD and the

general population, protective associations were found at relatively low intakes of alcohol, with no indications for further benefit of higher intakes.
For all-cause mortality, the conclusions of the DDG-2015 and in people with ASCVD are in line as well. The DDG-2015 conclusion was of a maximum risk reduction of 15% at 6 g alcohol per day. In people with ASCVD, no optimal intake within the range of 2-35 g/d could be pointed out with respect to all-cause mortality risk (and neither for other outcomes). The committee found 20% risk reduction at intakes between 2-35 g/d without indications of further benefit for increasing alcohol consumption within this range.

Within this intake range (2-35 g/d), harmful associations were reported for consumption of alcohol and/or alcoholic beverages (such as beer and liquor) with stroke and several types of cancer in the DDG-2015. There was no or too little evidence in people with ASCVD to draw conclusions on these outcomes in people with ASCVD. Given the observations reported in the DDG-2015 were derived from studies in the general population, that includes people with ASCVD, the committee assumes these observations are also of importance to people with ASCVD and should be taken into account in formulating recommendations on alcohol consumption for people with ASCVD.

In the DDG-2015, no differentiation in the recommendation for alcohol was made between men and women. In people with ASCVD, there were no indications found that associations with CVD outcomes and all-cause mortality would be substantially different in men and women, although there were less data in women available. Based on this, the committee sees no reason to give separate recommendations for men and women, which is in line with the current DDG-2015 recommendation.

3.4.2 Comparison with results of Wood et al.

In 2018, the study by Wood et al.[5] was published in the Lancet, which is considered a landmark paper by the committee. Therefore, the committee additionally compared its findings for people with ASCVD with the findings presented in this paper. This comparison does not impact the committee's recommendation on alcohol consumption for people with ASCVD.
This study by Wood et al. combined data of 83 prospective cohort studies that included 599912 current drinkers. During 5.4 million person-years of follow-up, 40310 cases of all-cause mortality and 39018 CVD events occurred. The main analyses were performed in alcohol consumers, and the intake category of 0-25 g/week was used as reference group for these analyses. Dose-response associations were calculated per 100 g per week of alcohol (which is on average 14 g/d).
For all-cause mortality, a linear, harmful association was found from intakes of 100 g/week. For intakes up to 100 g/week there was no difference with the reference group.

In an additional analysis, never drinkers and ex-drinkers were added to the analysis. In that analysis, a J-shape was observed, with never and ex-drinkers having a higher risk of mortality than alcohol consumers of 0-25 g/week. In comparison, the studies in people with ASCVD included non-drinkers in the analyses, and (all but one) used non-drinkers as reference group and showed a J-shaped association. This is in line with the findings of Wood et al. where never and ex-drinkers were taken into account. However, in people with ASCVD no statistically significant increased risk was found at higher intakes of alcohol (from 35 g/d) whereas Wood et al. found increased risks from 100 g/week. This may be explained by differences in characteristics of the study populations. People with ASCVD are relatively older, and possibly these are the healthy survivors and/or people with less alcohol-related risk-taking behaviour. Also, mortality due to MI may have been higher in the ASCVD population than the general population. This could be a potential explanation, as is further explained in the next paragraph.

For CVD outcomes, Wood et al. found a J-shaped association for total CVD, with the risk reducing up to 100 g alcohol consumption per week and increasing from intakes of 100 g per week and higher. Higher intakes of alcohol associated statistically significantly with increased risk of total CVD. However, there were differences in associations between CVD-subtypes. For the MI outcome (which accounted for the majority of CVD cases), there was, by approximation, a log-linear inverse association with alcohol consumption. For other CVD-subtypes, such as stroke and heart failure, there were, by approximation, linear harmful associations with alcohol consumption. In comparison, in the studies in people with ASCVD, the CVD morbidity and mortality was to a large extent due to MI. The conclusion of the committee, that moderate intakes of alcohol associate with a reduction in the risk of CVD events in people with ASCVD, is in line with the findings of Wood et al. Also, the committee found no evidence for increased risks of CVD outcomes with higher intakes of alcohol, although there were actually too few studies to draw a conclusion on this. This observation of no increased CVD risk is in line with the finding of Wood et al. for the MI outcome. MI may have accounted for a relatively large share of the CVD events in the studies in people with ASCVD (compared to the general population) since the majority of included participants had a prior MI and are therefore at higher risk for a subsequent MI.

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Annexes

A Search strategy and study selection

A.1 Search strategy

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

(Alcoholic beverages[MeSH] OR Alcohol abstinence[MeSH] OR Alcohol drinking[MeSH] OR wine[MeSH] OR beer[MeSH] OR (drinking behavior[MeSH] AND alcohol[TIAB]) OR (ethanol[MeSH] NOT (Ethamoxytriphetol[MeSH] OR ethanolamines[MeSH] OR ethanolamine[MeSH] OR Ethylene Chlorohydrin[MeSH] OR mercaptoethanol[MeSH] OR phenylethyl alcohol[MeSH] OR trifluoroethanol[MeSH])) OR Alcoholic[TIAB] OR Alcohol*[TIAB] OR Alcohol consumption[TIAB] OR Alcohol intake [TIAB] OR (drinking behavior[MeSH] AND alcohol*[TIAB]) OR (drinking behav*[TIAB] AND alcohol[TIAB]) OR beer[TIAB] OR wine[TIAB] OR spirits[TIAB] OR (ethanol[TIAB] NOT (Ethamoxytriphetol[TIAB] OR ethanolamines[TIAB] OR ethanolamine[TIAB] OR Ethylene Chlorohydrin[TIAB] OR mercaptoethanol[TIAB] OR

phenylethyl alcohol[TIAB] OR trifluoroethanol[TIAB])) NOT ("Non-alcoholic Fatty Liver Disease"[Mesh] OR Non-alcoholic Fatty Liver Disease[TIAB] OR Nonalcoholic Fatty Liver Disease[TIAB] OR “Motivational Interviewing"[Mesh]))

AND

(cohort studies[MeSH] OR cohort stud*[TIAB] OR longitudinal studies[MeSH] OR longitudinal stud*[TiAB] OR prospective studies[MeSH] OR prospective stud*[TIAB] OR “Observational study”[publication type] OR "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] NOT ("Systematic Review" [Publication Type] OR "Systematic Reviews as Topic"[Mesh] OR “Review”[Publication Type] OR "Meta-Analysis" [Publication Type] OR "Meta-Analysis as Topic"[Mesh] OR "Network Meta-Analysis"[Mesh] OR "Primary Prevention"[Mesh]))

Limit: after 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(“Alcoholic beverages”) OR TITLE-ABS(“Alcohol abstinence”) OR TITLE-ABS(“Alcohol drinking”) OR TITLE-ABS(wine) OR TITLE-ABS(beer) OR TITLE-ABS(spirits) OR TITLE-ABS(Alcoholic) OR TITLE-ABS(Alcohol*) OR TITLE-ABS(“Alcohol consumption”) OR TITLE-ABS(“Alcohol intake”)
OR
TITLE-ABS(“drinking behavior”) AND TITLE-ABS(alcohol*) OR TITLE-ABS(“drinking behav*”) AND TITLE-ABS(alcohol)
OR
TITLE-ABS(ethanol)
AND NOT
TITLE-ABS(Ethamoxytriphetol) OR TITLE-ABS(ethanolamines) OR TITLE-ABS(ethanolamine) OR TITLE-ABS(“Ethylene Chlorohydrin”) OR TITLE-ABS(mercaptoethanol) OR TITLE-ABS(“phenylethyl alcohol”) OR TITLE-ABS(trifluoroethanol)
AND NOT
TITLE-ABS("Non-alcoholic Fatty Liver Disease") OR TITLE-ABS(“Non-alcoholic Fatty Liver Disease”) OR TITLE-ABS(“Nonalcoholic Fatty Liver Disease”) OR TITLE-ABS(“Motivational Interviewing")

AND

TITLE-ABS-KEY(“cohort stud*”) OR TITLE-ABS-KEY(“longitudinal stud*”) OR TITLE-ABS-KEY(“prospective stud*”) OR TITLE-ABS-KEY(“Observational study”) OR 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(randomiszed) 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)

AND NOT

TITLE-ABS-KEY ("Systematic Review") OR TITLE-ABS-KEY (Review) OR TITLE-ABS-KEY ("Meta-Analysis") OR TITLE-ABS-KEY ("Meta Analysis") OR TITLE-ABS-KEY ("Network Meta-Analysis") OR TITLE-ABS-KEY ("Primary Prevention")

Limit: after 2000

A.2 Selection of individual cohort studies and RCTs

Step 1. Identification
8546 records retrieved:

- PubMed: 3709
- Scopus: 4837

2359 duplicates excluded

Step 2. Screening
6187 records screened,
6151 records excluded after first selection

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

- Already included in MA
- Different study population
- No exposure of interest
- No outcome of interest
- Alcohol measured dichotomously
- Pre-event alcohol assessment
- Different study design

Step 4. Inclusion
5 records included

B Results of MA Ding et al. and of individual studies

Supplemental Table B1 Summary of study characteristics and associations of alcohol consumption with risk of mortality and morbidity in people with ASCVD: meta-analysis of Ding et al.[6] (2021) of prospective cohort studies that measured alcohol consumption after the occurrence of the index-event

Aspect	Explanation
Study duration	UK Biobank mean/median follow-up of 8.7 y HSE/SHeSs mean/median follow-up of 9.5 y 9 cohort studies mean/median follow-up of 5.4 y 3 cohort studies max follow-up of 10 to 20 y
Number of studies	11
Dietary exposure	Average alcohol consumption in grammes per day
Dietary assessment method	Self-reported alcohol intake assessed at baseline: average weekly or monthly consumption of alcoholic beverages
Heterogeneity[b]	All-cause mortality and CVD mortality: I^2 = 0% Major cardiovascular events: I^2 = 75%
Strength of the association[c]: maximal effect size[d] (RR (95% CI) and g/day; reversion point[e] in g/day. Reference group: non-drinkers	ALL-CAUSE MORTALITY: - Alcohol consumption assessed post-event: max effect size RR 0.81 (0.74, 0.88), at 9 g/day; reversion point 52 g/day (n=8 studies, n=37,245 participants, n=6546 cases) CVD MORTALITY: - Alcohol consumption assessed post-event: max effect size RR 0.73 (0.60, 0.90), at 8 g/day; reversion point 43 g/day (n=7 studies, n=21,525 participants, n=2003 cases) MAJOR CARDIOVASCULAR EVENTS[a]: - Alcohol consumption assessed post-event: max effect size RR 0.50 (0.26, 0.96), at 6 g/day; reversion point 15 g/day (n=4 studies, n=28,621 participants, n=4050 cases)
Study population	People with a previous MI, angina, or stroke prior to baseline; - UK Biobank: BMI[h]: 29 ± 5 kg/m^2; medication: cholesterol-lowering (83%), antihypertensive (70%), antiplatelet agents (79%), digoxin (2%), warfarin (6%); men (71%) and women (29%); - HSE/SHeSs: BMI[h]: 28 ± 5 kg/m^2; medication: cholesterol-lowering (23%), antihypertensive (55%), antiplatelet agents (45%), digoxin (4%); men (57%) and women (43%); - Other studies: Population characteristics NR; Europe, USA, Canada, and Japan

Abbreviations: BMI: body mass index; CI: confidence interval; CVD: cardiovascular disease; HSE: Health Survey for England; MI: myocardial infarction; NR: not reported; RR: relative risk; SHeSs: Scottish Health Survey; UK: United Kingdom; USA: United States of America; y: years.

[a] Composite of angina, fatal and non-fatal MI and stroke, revascularization procedures (angioplasty or coronary artery bypass grafting), death from heart failure, and sudden cardiac death. Data for major cardiovascular events were only available from the UK Biobank and 3 other studies.

[b] Refers to the overall association (presented in the Table below).

[c] Statistical models were constructed using fractional polynomial regression, adjusting for at least age, sex, and smoking status, in order to determine the best-fitting dose-response association between alcohol and each outcome in the combined sample of participants from all studies.

[d] Maximal effect size defined as the lowest point of the dose-response curve within the range of doses reported in the studies.

[e] Reversion point defined as the dose of alcohol at which the inverse association is no longer statistically significant at the 95% CI.

[h] Mean ± standard deviation.

Supplemental Table B2 Summary of associations of alcohol consumption with risk of mortality and morbidity in people with cardiovascular disease: meta-analysis of Ding et al.[6] *(2021)* of prospective cohort studies

Aspect	Explanation
Strength of the association: maximal effect size[a] (RR (95% CI) and g/day; reversion point[b] in g/day. Reference group: non-drinkers.	ALL-CAUSE MORTALITY: - Overall: max effect size RR 0.79 (0.73, 0.85), 7 g/day; reversion point 62 g/day (n=11 studies) - Male: max effect size RR 0.82 (0.72, 0.93), 9 g/day; reversion point 39 g/day (n=6 studies) - Female: max effect size RR 0.64 (0.36, 1.14), 54 g/day; reversion point 49 g/day (n=3 studies) - MI as primary event: max effect size RR 0.82 (0.68, 0.99), 2 g/day; reversion point 7 g/day (n=9 studies, n=29,554 participants; n cases NR) - Angina as primary event: max effect size RR 0.79 (0.63, 0.99), 39 g/day; reversion point 46 g/day (n=2 studies) - Stroke as primary event: max effect size RR 0.71 (0.42, 1.20), 12 g/day; reversion point NA (n=3 studies, n=3618 participants; n cases NR) - Reference group including former drinkers: max effect size RR 0.77 (0.69, 0.85), 16 g/day; reversion point 75 g/day (n=9 studies) - Reference group excluding former drinkers: max effect size RR 0.85 (0.71, 1.00) and 3 g/day, reversion point 3 g/day (n=4 studies)

- Post-event alcohol assessment:
  max effect size RR 0.81 (0.74, 0.88) and 9 g/day, reversion point 52 g/day (n=8 studies)
- Multiple alcohol measures:
  max effect size RR 0.78 (0.59, 1.03), 16 g/day; reversion point NA (n=2 studies)

CVD MORTALITY:

- Overall:
  max effect size RR 0.73 (0.64, 0.83), 8 g/day; reversion point 50 g/day (n=9 studies)
- Male:
  max effect size RR 0.72 (0.62, 0.85), 9 g/day; reversion point 32 g/day (n=5 studies)
- Female:
  max effect size RR 0.29 (0.09, 1.01), 54 g/day; reversion point 54 g/day (n=2 studies)
- MI as primary event:
  max effect size RR 0.76 (0.64, 0.91), 3 g/day; reversion point 25 g/day (n=6 studies, n=12,422 participants; n cases NR)
- Angina as primary event:
  max effect size RR 0.72 (0.42, 1.23), 56 g/day; reversion point NA (n=2 studies)
- Stroke as primary event:
  max effect size RR 0.63 (0.37, 1.08), 26 g/day; reversion point NA (n=3 studies, n=3617 participants; n cases NR)
- Reference group including former drinkers:
  max effect size RR 0.73 (0.58, 0.93), 13 g/day; reversion point 27 g/day (n=6 studies)
- Reference group excluding former drinkers:
  max effect size RR 0.71 (0.55, 0.90) and 7 g/day, reversion point 29 g/day (n=5 studies)
- Post-event alcohol assessment:
  max effect size RR 0.73 (0.60, 0.90) and 8 g/day, reversion point 43 g/day (n=7 studies)
- Multiple alcohol measures:
  max effect size RR 0.58 (0.40, 0.84), 17 g/day; reversion point 33 g/day (n=1 study)

MAJOR CARDIOVASCULAR EVENTS [c]:

- Overall:
  max effect size RR 0.50 (0.26, 0.96), 6 g/day; reversion point 15 g/day (n=4 studies)
- Male:
  max effect size RR 0.56 (0.23, 1.34), 8 g/day; reversion point NA (n=3 studies)

	- Female: max effect size RR 0.67 (0.43, 1.05), 54 g/day; reversion point 49 g/day (n=1 study) - MI as primary event: max effect size RR 0.79 (0.66, 0.94), 11 g/day; reversion point 35 g/day (n=4 studies, n=20,361 participants; n cases NR) - Angina as primary event: max effect size RR 0.69 (0.59, 0.81), 35 g/day; reversion point NA (n=1 study) - Stroke as primary event: max effect size RR 0.49 (0.26, 0.92), 72 g/day; reversion point NA (n=1 study, n=1855 participants; n cases NR) - Reference group including former drinkers: max effect size RR 0.72 (0.53, 0.97), 40 g/day; reversion point 45 g/day (n=3 studies) - Reference group excluding former drinkers: max effect size RR 0.78 (0.46, 1.31) and 17 g/day, reversion point NA (n=2 studies) - Multiple alcohol measures: max effect size RR 0.32 (0.14, 0.71), 38 g/day; reversion point NA (n=1 study)

Abbreviations: CI: confidence interval; CVD: cardiovascular disease; MI: myocardial infarction; NA: not applicable; NR, not reported; RR: relative risk.

[a] Maximal effect size defined as the lowest point of the dose-response curve within the range of doses reported in the studies.

[b] Reversion point defined as the dose of alcohol at which protection against the outcome is no longer statistically significant at the 95% CI level; NA if non-significant association was found at any level of consumption or if the association remained statistically significant within the range of doses reported by the studies.

[c] Composite of angina, fatal and non-fatal MI and stroke, revascularization procedures (angioplasty or coronary artery bypass grafting), death from heart failure, and sudden cardiac death. Data for major cardiovascular events were only available from the UK Biobank and 3 other studies. These four studies all measured post-event alcohol consumption.

Table B3 Summary of associations of alcohol consumption with risk of mortality and morbidity in people with cardiovascular disease: individual prospective cohort studies of Bryson et al. and Cruijsen et al.[a]

Aspect	Bryson et al. 2006[9]	Cruijsen et al. 2021[7]
Study duration	7 to 10 years (range)	Median follow-up of 12.4 years
Primary event	CVD	CHD
Cohort name	Cardiovascular Health Study (CHS)	Alpha Omega Cohort
Exposure (alcohol consumption)	Categorised into: never drinkers, former drinkers, <1 drink/week, 1 to 6 drinks/week, 7 to 13 drinks/week, >14 drinks/week. One drink defined as a 12-oz beer, a 6-oz glass of wine, or a shot of liquor.	Categorised into: abstainers, very light drinkers (>0-2 g/day), light drinkers (male: >2-10 g/day, female: >2-5 g/day), moderate drinkers (male: >10-30 g/day, female >5-15 g/day), heavy drinkers (male: >30 g/day, female: >15 g/day)

Dietary assessment method	Weekly alcohol intake assessed at baseline, and at follow-up years 2 through 5, and 7 through 9 (no further details provided)	FFQ at baseline assessing frequency and quantity of alcohol intake during the previous month. The FFQ was an extended version of a reproducible and biomarker-validated FFQ (Pearson correlation coefficient between FFQ and dietary history method 0.83 for total energy intake; for alcohol intake NR; correlation for alcohol intake between FFQ and a lifestyle questionnaire was 0.81.)
Health outcome	Incident CHF Incident CHF and cardiovascular death	All-cause mortality Cardiovascular mortality IHD mortality
Number of participants; number of cases	5595 participants; Incident CHF: 1056 Incident CHF and cardiovascular death: NR	3891 participants[c]; All-cause mortality: 1774 Cardiovascular mortality: 791 IHD mortality: 487
Strength of association: HR (95% CI)	Relative to abstainers: INCIDENT CHF: - Former drinkers: HR 1.51 (1.23, 1.85) - <1 drink/week: HR 0.90 (0.75, 1.08) - 1 to 6 drinks/week: HR 0.82 (0.67, 1.00) - 7 to 13 drinks/week: HR 0.66 (0.47, 0.91) - 14+ drinks/week: HR 0.87 (0.67, 1.14) INCIDENT CHF AND CARDIOVASCULAR DEATH: - Former drinkers: NR - <1 drink/week: HR 0.94 (0.82, 1.08) - 1 to 6 drinks/week: HR 0.84 (0.72, 0.98) - 7 to 13 drinks/week: HR 0.70 (0.54, 0.98) - 14+ drinks/week: HR 0.79 (0.64, 0.98)	Relative to (combined) reference group of abstainers and very light drinkers[c]: ALL-CAUSE MORTALITY: - Light drinkers: HR 0.93 (0.81, 1.06) - Moderate drinkers: HR 0.90 (0.79, 1.03) - Heavy drinkers: HR 0.98 (0.84, 1.14) CARDIOVASCULAR MORTALITY: - Light drinkers: HR 0.78 (0.64, 0.95) - Moderate drinkers: HR 0.81 (0.67, 0.98) - Heavy drinkers: HR 0.86 (0.68, 1.08) IHD MORTALITY: - Light drinkers: HR 0.76 (0.59, 0.98) - Moderate drinkers: HR 0.78 (0.61, 1.00) - Heavy drinkers: HR 0.91 (0.69, 1.20)
Study population	People with prevalent cardiovascular disease at baseline (MI, angina, stroke, TIA, claudication); BMI[b]: 26 kg/m^2; medication: NR; men (42%) and women (58%); USA	People with a history of MI; BMI[b]: 28 ±4, medication: antihypertensive medication (90%), lipid-modifying medication (87%); men (79%) and women (21%); Europe (The Netherlands)

Abbreviations: BMI: body mass index; CHD: coronary heart disease; CHF: congestive heart failure; CI: confidence interval; CVD: cardiovascular disease; FFQ: food frequency questionnaire; HR: hazard ratio; IHD: ischemic heart disease; MI: myocardial infarction; NR: not reported; USA: United States of America.

[a] The following confounders were included in the multivariable models: Bryson et al.: age, race, gender, smoking status, education, income, marital status, exercise intensity, diabetes status, and BMI; Cruijsen et al.: age, sex, education level, smoking status, obesity, physical activity, energy intake excluding energy from alcohol, sugar sweetened beverages, red and processed meat, whole grains, fruits, vegetables, coffee, tea, milk, fish and salt from foods.

[b] Mean ± standard deviation.

[c] Refers to the associations where the reference group excludes former drinkers.

Table B4 Summary of associations of alcohol consumption with risk of mortality and morbidity in people with cardiovascular disease: individual prospective cohort studies of Iestra et al. and Mukamal et al.[a]

Aspect	Iestra et al. 2006[8]	Mukamal et al. 20061[5]
Study duration	Mean follow-up of 10 years	Mean follow-up of 4.3 years
Primary event	CHD	CHD
Cohort name	Healthy Ageing: a Longitudinal study in Europe (HALE)	Post-CABG trial
Exposure (alcohol consumption)	Categorised into: abstainers (<1g/day), moderate drinkers (1-20 g/day for women and 1-30 g/day for men), excessive drinkers (>20 g/day for women and >30 g/day for men)	Categorised into: abstainers (<1 drink/week), light drinkers (1-6 drinks/week), moderate drinkers (7-13 drinks/week), heavier drinkers (≥ 14 drinks/week). One standard drink specified as a 5-ounce glass of wine, 12 ounces of beer, or a single mixed drink).
Dietary assessment method	Self-reported alcohol consumption at baseline (no further details provided)	Self-reported usual weekly alcohol consumption assessed at baseline. Validated against levels of HDL-C (Spearman correlation coefficient 0.23).
Health outcome	All-cause mortality	Graft progression (assessed angiographically) Clinical events (composite endpoint of death from cardiovascular or unknown causes, non-fatal MI, stroke, bypass surgery, or angioplasty)
Number of participants; number of cases	426 participants; All-cause mortality: 247	1351 participants; Graft progression: NR Clinical events: 238
Strength of association: HR or OR (95% CI)	For consumers relative to abstainers: ALL-CAUSE MORTALITY: - HR 0.77 (0.58, 1.02)	Relative to abstainers: GRAFT PROGRESSION: - Light drinkers: OR 0.90 (0.70, 1.10) - Moderate drinkers: OR 0.70 (0.50, 1.10) - Heavier drinkers: OR 0.90 (0.60, 1.30) CLINICAL EVENTS:

		- Light drinkers: HR 1.00 (0.70, 1.30) - Moderate drinkers: HR 0.70 (0.40, 1.10) - Heavier drinkers: HR 1.20 (0.70, 1.90)
Study population	People with a history of MI; Body weight status: 21% obese; medication NR; men (67%) and women (33%); Europe	Patients who underwent CABG; BMI[b]: 28 ± 4; medication: NR; men (92%) and women (8%); Canada/USA

Abbreviations: BMI: body mass index; CABG: coronary artery bypass grafting; CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; HDL-C: high-density lipoprotein cholesterol, HR: hazard ratio; MI: myocardial infarction; NR: not reported; OR: odds ratio; USA: United States of America.

[a] The following confounders were included in the multivariable models: Iestra et al: study (FINE, SENECA), gender, age, years of education, body mass index, history of diabetes or stroke; Mukamal et al: age, years since CABG, sex, race, RCT treatment assignment, BMI, physical activity, current smoking, former smoking, history of MI, history of hypertension, history of stroke, and intake of energy, fat, and protein.

[b] Mean ± standard deviation.

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