Fish

No. 2023/02Ce, 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 fish 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 Fish

This background document describes the scientific evidence regarding fish intake. Fish is an important source of the very-long-chain polyunsaturated fatty acids eicosapentaenoic acid and docosahexaenoic acid (the fish fatty acids EPA and DHA) and essential nutrients such as vitamin D, iodine and selenium. Oily fish species include herring, salmon and mackerel. Non-oily fish species include pollock, cod, plaice, and the Pangas catfish.

1.2 Fish recommendation and intake in the Netherlands

The Health Council of the Netherlands included a guideline for fish consumption in the *Dutch dietary guidelines 2015*, which is as follows: 'Eat fish weekly, preferably oily fish'.[2] In the Netherlands, people consume on average 15 grammes of fish and fish products a day.[3]

2 Methodology

2.1 Question

The Committee aimed to answer the following question: What is the relationship (effect or association) of relatively higher fish consumption compared to no or relatively lower fish 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) because it assumes that the majority of this population will have ASCVD.

2.3 Nutritional topics

The Committee searched for studies into the effects or associations of fish consumption on or with health outcomes. In its evaluation, the Committee could not distinguish between the type of fish (e.g., lean fish, oily fish; or separated by preparation method) since such information was generally not available in the evaluated literature. Shellfish is not considered fish by the Committee. However, several studies defined shellfish as part of the fish exposure. Given that shellfish usually takes a small share in total fish consumption, the Committee did not exclude such studies from its evaluation.

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)
  - atrial fibrillation
  - 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)

In line with the approach taken with the *Dutch dietary guidelines 2015*, the Committee aimed to distinguish between fatal CHD, non-fatal CHD and sudden (cardiac) death in its evaluation, since there are indications that fish and fish fatty acids in particular protect against fatal CHD and sudden (cardiac) death.[5]
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

2.5.1 Search and selection of studies

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 between fish intake and the above-mentioned health outcomes in people with ASCVD. To identify such publications, the Committee searched PubMed and Scopus in August 2021. This search yielded no relevant publications. Next, individual cohort studies and RCTs were searched in PubMed and

Scopus in September 2021. The search strategy and specification of the study selection are presented in Annex A.

One pooled analysis of 3 prospective cohort studies and 4individual prospective cohort studies were selected for the Committee's evaluation. Two additional prospective cohorts were selected via the searches for literature on other nutritional topics that were evaluated for the current advisory report (meat, dairy). Moreovers, one cohort study was found via the Committee's network. Regarding RCTs, 4 reports of individual RCTs were selected for evaluation via the Committee's literature search and one additional RCT was selected via the search for literature on another nutritional topic that was evaluated for the current advisory report (saturated fat substitution).

Where it was possible and considered helpful to formulate conclusions on fish consumption with health outcomes, the Committee pooled estimates of the selected studies, using a random effects meta-analysis approach. The Committee combined studies with the following categories of fish consumption: high versus low (i.e., the highest intake category compared to the reference group with the lowest intake); average consumption of 1 portion per week versus no or occasional consumption of fish; average consumption of 2 portions a week versus no or occasional consumption of fish; and average consumption of 3 to 6 portions a week versus no or occasional consumption of fish. The weekly average consumption of fish was based on reported averages or medians in the study reports or, in case this information was not available, on midpoints of reported categories of intake, and/or on 1.2 times the lower bound of an open ended upper intake category.[6] For the analyses, the Committee assumed that one portion of fish is 100 g. Two studies reported on continuous associations of fish consumption with health outcomes. The study of Trichopoulou et al.[7] reported on the association per 35 g/d increment of fish intake with risk of all-cause mortality. The authors did not report on the shape of the association, and therefore there was uncertainty as to whether the association was linear and whether converting this HR to a categorical HR would be appropriate. The Committee added the study in an additional analysis, assuming there was a linear association. Based on this assumption, the HR presented by Trichopoulou et al. was interpreted as the risk for all-cause mortality for 2.5 portions of fish a week (which is on average 35 g/d) versus no fish consumption. The impact of this study on the overall result was discussed in the accompanying text. Second, the study by Stewart et al.[8] reported one risk estimate, of 0.90, that reflected the HR per category increment of fish consumption (never/rarely, once a week, several times a week, 1-2 servings a day). Deviation from linearity was checked by the authors, and no such deviation was reported. This HR was converted into HRs per category of fish consumption by interpreting the HR reported by Stewart et al. reflected the association of consumption of 1 portion of fish a week versus never/rarely, and then subsequently multiplying the HR and 95%CI by this HR of 0.90

to calculate HRs and 95%CIs for the subsequent categories of fish consumption. It should be noted that this likely leads to overestimation of the precision of the associations. Due to this, the study by Stewart et al. was added in an additional analysis, and the impact of this study on the overall result was discussed in the accompanying text.

2.5.2 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 fish intake 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 fish consumption

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

3.1 RCTs

Table 1 summarises the results and characteristics of individual RCTs that provided evidence regarding the effects of fish consumption on mortality and cardiovascular health outcomes in people with ASCVD. The Committee notes these RCTs (of Burr et al.[9,10]) were also selected for the *Dutch dietary guidelines 2015* evaluation of fish.[5] Moreover, the 1989 study of Burr et al. [10] was used as proof of principle study to support the cohort findings of a protective association of fish consumption with reduced risk of fatal CHD for the *Dutch dietary guidelines 2015*.[2]

One report of an RCT reported results on depression as outcome.[11] These results were derived from the same RCT as the results on mortality and cardiovascular health from Burr et al.[9] (2003; described in the table and text below). In addition, two reports of small-scale, short term RCTs reported results on the outcome of LDL cholesterol, blood pressure and BMI.[12,13] Given no other studies were found on the outcomes of depression, LDL cholesterol, blood pressure or BMI, and therefore no conclusions can be drawn on these outcomes, these studies were not summarised below.

Table 1 Summary of effects of fish consumption on health outcomes in people with atherosclerotic cardiovascular disease: RCTs

Aspect	Burr et al., 1989[10]	Burr et al., 2003[9]
Study duration	2 years	3 to 9 years
N participants in intervention (i); and control (c) group; N cases in i; and c group	i: 1015, c: 1018 All-cause mortality: i: 94, c: 130 CHD events: i: 127, c: 149 CHD mortality: i: 78, c: 116 Non-fatal MI: i: 49, c: 33	i: 764, c: 764 All-cause mortality: i: 141, c: 109 CHD mortality: i: 94, c: 67 Sudden cardiac death: i: 42; c: 17
Study design	Parallel 4-arm RCT	Parallel 4-arm RCT
Diet of intervention (i) and control (c) group	i: advice to eat two weekly portions of oily fish (200-400 g). People who did not tolerate fish were given 1.5 g/d Maxepa supplements c: non-specific advice that did not include the intervention	i: advice to eat at least two portions of oily fish/w, or to take up to 3g of fish oil as a partial or total substitute (when participant found fish unpalatable) c: 'sensible eating' – non-specific advice that did not include the intervention
Strength of the effects[a]	All-cause mortality: HR 0.71 (95%CI 0.54, 0.92) CHD events: HR 0.84 (95%CI 0.66, 1.07) CHD mortality:	All-cause mortality: HR 1.15 (95%CI 0.96, 1.36) CHD mortality: HR 1.26 (95%CI 1.00, 1.58) Sudden cardiac death:

	RR 0.68 (*P*<0.01)[b] Non-fatal MI: RR 1.5 (*P*=NR)[c]	HR 1.54 (95%CI 1.06, 2.23)
Study population	Men <70 years with who survived MI; BMI: NR; medication: beta-blockers (29%), other hypertensive (34%), antiangina (47%), anticoagulant (5%), aspirin/ antiplatelet (10%), digoxin/ antiarrhythmic (10%); men; UK	Men <70 years with stable angina; BMI: 28 ± 4 kg/m^2; medication: beta-blockers (42%), nitrates (%NR), digoxin (%NR), lipid-lowering drugs (%NR), anticoagulants (%NR), diuretics (%NR); men; UK

Abbreviations: BMI: body mass index; CHD: coronary heart disease; CI: confidence interval; HR: hazard ratio; MI: myocardial infarction; NR: not reported; RCT: randomised controlled trial; RR, relative risk; UK: United Kingdom; w: week.

[a] The presented effects were adjusted for: Burr et al. (1989): history of MI, angina, or hypertension; X-ray evidence of cardiomegaly, pulmonary congestion, or pulmonary oedema, treatment (at entry) with beta-blockers, other antihypertensives, digoxin/ antiarrhythmics, or anticoagulants; Burr et al. (2003): age, smoking, previous MI, history of high blood pressure, diabetes, BMI, serum cholesterol, medication, fruits advice.

[b] The authors reported the *p*-value for the effect of fish advice on CHD mortality, whereas the RR/HR was not reported. Therefore, the Committee itself calculated the RR by dividing the percentage of cases in the intervention group with the percentage of cases in the control group (7.7/11.4).

[c] The authors reported no *p*-value or RR/HR for the effect of fish advice on the incidence of non-fatal MI. The RR was calculated by the Committee itself by dividing the percentage of cases in the intervention group with percentage of cases in the control group (4.8/3.2).

Conclusion:

There is too little research from RCTs to draw conclusions regarding the effects of fish intake on the risk of all-cause mortality and CHD morbidity or 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: There are no MAs of RCTs that address the effects of fish consumption on risk of all-cause mortality, CHD morbidity and/or mortality. There are two RCTs that reported on effects on all-cause mortality and CHD mortality.[9,10] These two studies showed contradictory results on these outcomes, with one study showing protective effects[10], and the other study showing (a tendency towards) harmful effects.[9] The Committee noted methodological concerns with respect to one of the studies[9], and these limited the Committee to draw conclusions based on this study. This leaves one study of sufficient quality which is[10], on its own, too little to base conclusions on. The Committee concluded there is too little research. Nevertheless, it should be noted this single study of sufficient quality can be used as supportive evidence (proof of principle RCT) for protective associations with strong evidence in cohort studies (further explained in the background document *Methodology for the evaluation of the evidence*[4]).

Explanation:

Two RCTs were found and are briefly described below.

Firstly, the Diet and Reinfarction Trial (DART; Burr et al. 1989)[10] found a 29% reduced risk of all-cause mortality and 32% reduced risk of CHD mortality in men who survived a previous MI and consumed 200 – 400 g/d of oily fish compared to those who did not. No effect was found for CHD events. The RCT also tested the effects for fibre (fruits and vegetables) using a 2x2 factorial design. Enrolment happened after an average of 41 days after surviving an MI in 2033 men. Oily fish advice included mackerel, herring, kipper, pilchard, sardine, salmon or trout. Compliance was measured by collecting 7-day weighed intake records in 25% of participants. The intakes were reported to correlate well with the intervention, but numerical results were not reported. At 6 months after start of the trial 14% of participants took Maxepa capsules as a partial or total substitute for oily fish. At 2 years this was 22%. Multiple confounding factors were added to the statistical model to correct for the slightly unbalanced characteristics of the randomised groups.
Fish oil supplements (Maxepa capsules) were provided by Seven Seas Health Care. The involvement of the sponsor was not reported and therefore the impact on the study findings remains unclear. Conflicts of interest of the authors were not reported.

Second, the RCT by Burr et al. [9] (2003) aimed to replicate findings from DART, and therefore set up a study with a similar design (DART II). Burr et al. examined whether all-cause mortality and sudden cardiac death could be reduced by fish consumption advice in men with angina. This study population was specifically chosen, since people with angina have a higher risk for CHD mortality. The study found no differences in risk of all-cause mortality and a borderline statistically significant increased risk of 26% (95%CI 1.00, 1.58) for fatal CHD. The increased risk was largely located among men who took fish oil supplements.
Whether shellfish fell under fish advice is not clear. The mean fish consumption of study subjects was not reported, however the mean change in EPA intake was 2.65 ± 1.35 g/w (from 0.67 ±0.53 g/week at baseline to 3.32 ± 1.35 g/w at 6 months) in the intervention group and 0.12 ± 0.76 g/w (from 0.66 ± 0.55 g/w at baseline to 0.78 ± 0.80 g/w at 6 months) in the control group. The authors provided multiple possible explanations for the unexpected findings, but none of these could be proven.[5,9] Also, the authors performed subgroup analyses by use of certain medications to search for a potential explanation. They found that the harmful association of fish advice was only present in people who did not use beta-blockers, and in people who used digoxin. However, the authors warned to be very careful with the interpretations of these findings since there was no prior hypothesis. Also, the subgroup of people taking digoxin was a rather small.
The study received extensive criticism related to design issues and lack of blinding.[14] In line with this, the Committee also noted concerns that may downgrade the quality of the study. These concerns limited the Committee to draw conclusions from this study. Particularly, it is of note that the inclusion to the study was temporarily stopped after 2

years because of financial problems. The inclusion reconvened after 1 year but with adaptations in the design. These included that participants in the fish advice group were subrandomised to receive fish advice or to take fish oil supplements. Also, there was reduced contact with the dietician. In the Committee's view, this may have contributed to limited re-inforcement of the dietary advice during the follow-up of the study. In addition, the assessment of compliance by means of blood fatty acid levels was performed in only 2% of participants at 6 months follow-up only. The long-term compliance was not reported. The Committee also notes the study was not blinded and it therefore cannot be excluded this influenced the behaviours of the participants and/or their physicians with respect to (advices on) medication use, dietary and other lifestyle factors. Unfortunately, it was not reported whether there were long-term changes in medication use and health related behaviours during the follow-up of the study. In their editorial comment on the DART-2 trial, Kris-Etherton et al.[14], note that the difference in reported fish intake at 6 months follow-up was rather small. They argued that, in the ensuing years with the increasing media coverage of the benefits of fish oils, control participants might have increased their fish intake or started taking supplements. Again, this could not be proven, but according to the Committee's view this leaves doubt about the interpretation of the study results.
The study was sponsored by, Seven Seas, a company that produces (among other things) fish oil capsules, and by the Fish Foundation, among other sponsors. The involvement of the sponsors was not reported and therefore the impact on the study findings remains unclear. Conflicts of interest of the authors were not reported.

3.2 Prospective cohort studies

Table 2 summarises the characteristics of prospective cohort studies that provided evidence regarding the associations of fish consumption with long-term health outcomes in people with ASCVD. The results of the selected studies were meta-analysed by the Committee, where possible and relevant. The pooled estimates for the all-cause mortality, total CVD, CVD mortality, MI and sudden cardiac death outcomes are presented in Table 3. Estimates per study for the stroke, CHD events and CHD mortality outcomes are presented in Table 4. In Annex B, the characteristics and results of the individual prospective cohort studies that were used for the Committee's evaluation are presented in detail.

Table 2 The associations of fish consumption with health outcomes in people with ASCVD: meta-analyses of cohort studies

Aspect	Explanation
Number of studies	10 cohort studies 8 for the outcome all-cause mortality 5 for the outcome total CVD 4 for the outcome CVD mortality

	4 for the outcome MI 3 for the outcome sudden cardiac death
Number of participants (p) and cases (c)	Outcome all-cause mortality: p: 60546; c: 9310 Outcome total CVD: p: 55206; c: 8154 Outcome CVD mortality: p: 43376; c >3099 (n cases not reported in one of the three studies) Outcome MI: p: 41721; c: >1762 (n cases not reported in one of the four studies) Outcome sudden cardiac death: p: 39309; c: >431 (n cases not reported in one of the three studies)
Study durations	Studies reported the mean or median follow-up, which ranged from to 3.7 to 12 years. 1 study reported 60008 person years.
Dietary exposure	There were estimates reported for 3 or more categories of fish consumption (7 studies) or categorised into below or above median (1 study) or continuously (2 studies).
Dietary assessment method	Fish consumption measured by validated FFQ (6 studies), self-reported 4-day food record (1 study), simple dietary frequency questionnaire (1 study), validated dietary history (1 study), FFQ or quantitative dietary questionnaire (1 study); All studies assessed fish consumption after the occurrence of the index-ASCVD-event.
Strength of the effect	Shown in Table 3
Study population	People with CVD (3 studies) or CHD (7 studies); average BMI: 26-28 kg/m^2; medication use: NR in 4 of the studies; statin use in the remaining studies ranged from 20-97% at baseline; regions: Europe, Asia, South America, Africa, North America, Oceania.

Abbreviations: ASCVD: atherosclerotic vascular disease; BMI: body mass index; CHD: coronary artery disease; CVD: cardiovascular disease; FFQ: food frequency questionnaire; MA: meta-analysis; MI: myocardial infarction; NR: not reported.

Table 3 Pooled RRs (95%CI) from prospective cohort studies for the associations of high versus low, and different portions of fish consumption compared to no consumption with health outcomes, with I^2 indicating the extent of heterogeneity, and *n* indicating the number of studies included

Outcome	High vs. low intake[a]	1 portion/week vs. no consumption[h]	2 portions/week vs. no consumption[i]	3-6 portions/week vs. no consumption[j]
All-cause mortality	b. 0.85 (0.77, 0.93), I^2 19%, n=8 c. 0.84 (0.77, 0.93), I^2 30%, n=7 d. 0.85 (0.77, 0.95), I^2 30%, n=7 e. 0.88 (0.80, 0.98), I^2 54%, n=9	b. 0.95 (0.88, 1.02), I^2 17%, n=5	b. 0.88 (0.81, 0.96), I^2 0%, n=6 e. 0.91 (0.83, 1.00), I^2 49%, n=7	b. 0.85 (0.76, 0.95), I^2 43%, n=6

All-cause mortality, excluding studies without adjustment for energy intake	b. 0.86 (0.77, 0.96), I^2 33%, n=6	b. 0.97 (0.89, 1.05), I^2 6%, n=4	b. 0.90 (0.82, 0.99), I^2 6%, n=5	b. 0.87 (0.77, 0.99), I^2 47%, n=5
All-cause mortality, excluding studies without adjustment for medication use	b. 0.86 (0.77, 0.95), I^2 9%, n=6	NA (all studies adjusted for medication use)	b. 0.88 (0.81, 0.96), I^2 5%, n=5	b. 0.86 (0.77, 0.96), I^2 29%, n=5
CVD events (total CVD)	b. 0.89 (0.80, 0.99), I^2 22%, n=4 f. 0.81 (0.70, 0.94), I^2 74%, n=5	b. 0.97 (0.89, 1.06), I^2 0%, n=3 f. 0.93 (0.88, 0.99), I^2 0%, n=4	b. 0.87 (0.79, 0.96), I^2 0%, n=4	b. 0.89 (0.80, 0.99), I^2 22%, n=4 f. 0.84 (0.77, 0.92), I^2 37%, n=5
CVD events, excluding studies without adjustment for energy intake	NA (all studies adjusted for energy intake)	NA (all studies adjusted for energy intake)	NA (all studies adjusted for energy intake)	NA (all studies adjusted for energy intake)
CVD events, excluding studies without adjustment for medication use	b. 0.90 (0.81, 1.00), I^2 0%, n=3	NA (all studies adjusted for energy intake)	b. 0.88 (0.79, 0.97), I^2 0%, n=3	b. 0.90 (0.81, 1.00), I^2 0%, n=3
CVD mortality[g]	b. 0.82 (0.71, 0.92) , I^2 0%, n=4	b. 0.97 (0.88, 1.06) , I^2 0%, n=4	b. 0.87 (0.77, 0.99), I^2 0%, n=4	b. 0.82 (0.71, 0.92) , I^2 0%, n=4
MI[g]	b. 0.83 (0.70, 0.97), I^2 0%, n=4	b. 0.89 (0.78, 1.03), I^2 0%, n=3	b. 0.89 (0.75, 1.05), I^2 0%, n=3	b. 0.81 (0.67, 0.97), I^2 0%, n=3
Sudden cardiac death[g]	b. 0.94 (0.62, 1.40), I^2 0%, n=3	b. 0.63 (0.20, 2.03), I^2 79%, n=3	b. 1.03 (0.72, 1.49), I^2 0%, n=3	b. 0.94 (0.62, 1.40), I^2 0%, n=3

Abbreviations: CVD: cardiovascular disease; MI, myocardial infarction; NA, not applicable; vs: versus.

[a] High consumption varied between 2.3 and 13.9 portions per week between the studies, of which one study addressed 13.9 portions per week on average (only included in all-cause mortality and MI analyses) and the remaining studies between 2.3 and 5.9 portions per week on average in analysis b. The study with 13.9 portions was excluded in analysis c. Low consumption varied between 0 and 2.9 portions per week between the studies, of which one study addressed 2.9 portions (only included in all-cause mortality and MI analyses), one study 1 portion (only included in the all-cause mortality analyses) on average and the remaining 0 or <0.1 portion per week in analysis b. The studies with 2.9 and 1 portion(s) per week were excluded in analyses c and d.

b Main result.

c Excluding the study of Manger et al.[15]

d Excluding the study of Iestra et al.[16]

e Adding the study of Trichopoulou et al.[7]

f Adding the study of Stewart et al.[8]

[g] Sensitivity analyses excluding studies without adjustment for energy intake and medications use were NA since all studies adjusted for energy intake and medication use.

[h] Reported average or midpoint fish intakes were 0.7 (1 study), 1.0 (2 studies) and 1.2 (2 studies) portions per week in analysis b. Lowest and highest fish intakes in this intake category ranged from 0.3 to 1.4 portions per week in the included studies in analysis b. With no consumption it is meant: no or occasional fish consumption.

[i] Reported average, median or midpoint fish intakes were 1.9 (1 study), 2.0 (2 studies), 2.3 (1 study) and 2.4 (2 studies)

portions per week in analysis b. Lowest and highest fish intakes in this intake category ranged from >1.4 to 2.8 portions per week in 5 of the included studies, and between 0.01 and 4 portions per week in one of the included studies (this latter study made a very small contribution to the pooled results) in analysis b. With no consumption it is meant: no or occasional fish consumption.

[j] Reported average or midpoint fish intakes were 3.1 (1 study), 3.6 (1 study), 3.6 (1 study), 4.5 (2 studies) and 4.8 (1 study) and 5.9 (1 study) portions per week in analysis b. Lowest and highest fish intakes in this intake category ranged from > 2.0 to 10.5 portions per week in the included studies in analysis b. With no consumption it is meant: no or occasional fish consumption.

Table 4 Associations of fish consumption with stroke, CHD events and CHD mortality in people with ASCVD, results from individual cohort studies[a]

Outcome	Author/ Study name	HR (95%CI) for high vs. low intake[b]; N participants; N cases	HR (95%CI) for 1 portion/week vs. no consumption[c]; N participants; N cases	HR (95%CI) for 2 portions/week vs. no consumption[c]; N participants; N cases	HR (95%CI) for 3-6 portions/week vs. no consumption[c]; N participants; N cases
Stroke	PURE[17]	0.91 (0.66, 1.27); NR	1.00 (0.80, 1.25); NR	0.75 (0.55, 1.03); NR	0.91 (0.66, 1.27); NR
Stroke	O/T[17]	1.25 (1.00, 1.58); 4978; 252	1.11 (0.91, 1.36); 16377; 740	0.99 (0.80, 1.24); 7335; 285	1.25 (1.00, 1.58); 4978; 252
CHD events (total CHD)	Erkilla et al.[18]	0.49 (0.17, 1.41); 150; 10	NA	1.00 (0.38, 2.66); 147; 14	0.49 (0.17, 1.41); 150; 10
CHD events (total CHD)	Manger et al.[15]	1.04 (0.74, 1.45); 603; 70	NA	NA	NA
CHD mortality	Pertiwi et al.[19]	0.74 (0.53, 1.03); 473; 48	0.85 (0.70, 1.04); 2069; 253	0.73 (0.54, 0.99); 523; 59	0.74 (0.53, 1.03); 473; 48
CHD mortality	Erkilla et al.[18]	1.04 (0.25, 4.31); 150; 6	NA	1.59 (0.39, 6.49); 147; 5	1.04 (0.25, 4.31); 150; 6
CHD mortality	Manger et al.[15]	1.03 (0.54, 1.94); 603; 19	NA	NA	NA

Abbreviations: CHD: coronary heart disease; NA: not applicable (this number of fish portions was not evaluated in the particular study) O/T: Ontarget/Trancend[17].

[a] These studies were not pooled by the Committee since they were too few to lead to conclusions with strong evidence.

[b] High consumption varied between 2 and 14 portions per week between the studies. Low consumption varied between 0 and 3 portions per week between the studies.

[c] With no consumption it is meant: no or occasional fish consumption.

Conclusion:

Cohort studies show that people with ASCVD with a relatively high compared to a relatively low consumption of fish have an approximate 15% lower risk of all-cause mortality. Most studies addressed intakes between 2 and 6 portions of fish

per week compared to no or occasional fish consumption. These studies show that people with ASCVD who consume 2 to 6 portions a week have an approximate 10 to 15% reduced risk of all-cause mortality. The evidence is strong.
Cohort studies show that people who consume 1 portion of fish a week likely have no difference in risk of all-cause mortality compared to people who consume no fish or only consume fish occasionally.

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 addressed the association of fish consumption with all-cause mortality[17,20,18,15,16,7,19], with a total of > 500 events counted in these studies. 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 8 of these cohort studies[17,20,18,15,16,19] showed a statistically significant reduction in the risks of all-cause mortality with relatively high compared to relatively low intakes of fish, without evidence for heterogeneity (I^2 19%). The definitions of low and high differed substantially per study and ranged from 2 to 14 portions per week (high) to 0 to 3 portions per week (low), with both categories including intakes of 2 and 3 portions per week. Therefore, the Committee did not quantify this conclusion in terms of quantities of fish intake. Most of the studies compared average intakes of 2 to 6 portions (in different categories) per week to no or occasional consumption of fish. The pooled results for comparisons of 2 and 3 to 6 portions per week to no or occasional consumption of fish were not materially different from each other and suggest there may be benefit of consuming 2 portions of fish a week, and there is no further benefit of increasing fish consumption from 2 up to 6 portions a week. For the category of 1 portion of fish there was no association with all-cause mortality risk.
   An eighth' study (Trichopoulou et al.[7]) addressed fish consumption continuously (per 35 g/d increment, which is equivalent to approximately 2.5 portions a week) in relation to all-cause mortality, as an additional analysis (Mediterranean diet was the main exposure of the study). This study found no association between fish consumption and risk of all-cause mortality. The Committee added the study in an additional analysis in which the HR for the continuous association was interpreted as the risk for all-cause mortality for approximately two portions of fish a week versus no fish consumption. This slightly attenuated the association for high versus low fish intake but did not substantially impact the conclusion. Adding the study to

the MA for 2 versus 0 portions of fish per week again slightly attenuated the association. In both analyses, it increased heterogeneity (particularly for 2 versus 0 portions of fish it substantially increased, with I^2 increasing from 0 to 49%). Possibly, the heterogeneity may be partly caused by overestimation of precision as a consequence of the conversion to the categorical interpretation. Also, it is unclear whether the reported association was linear (it was not reported whether deviation from linearity was checked by the authors). In case of deviation from linearity, the reported association may not be a good reflection of the association of fish consumption with all-cause mortality. This may have contributed to heterogeneity as well.

The average fish consumption varied substantially between studies, with average fish intakes in the highest intake categories ranging from 2 to 14 portions a week. In particular, it is noticeable that the average fish consumption in the study by Manger et al.[15] was rather high (ranging from on average 41 g/d in the reference group to 198 g/d in the highest intake group). There was no association of relatively higher compared to relatively lower fish consumption with all-cause mortality in that study, possibly due to the high fish intake. However, that study made a relatively small contribution to the total evidence base and excluding the study did not impact the overall result. Moreover, the study by Iestra et al. analysed fish consumption dichotomised into below and above the median fish intake of the study population. Due to this, the average fish consumption of the reference group was relatively high compared to the other studies (except Manger et al.), that used non-consumers and/or occasional consumers of fish as reference group. However, excluding the study by Iestra et al. did not impact the pooled result.

3. Considerations regarding the quality of the evidence:
   Two of the individual cohort studies did not adjust the analyses for energy intake (Barzi et al.[20] and Manger et al.[15]), and two did not adjust for the use of cholesterol- and blood pressure lowering medication (Erkilla et al.[18] and Iestra et al.[16]). Discarding these studies did not substantially change the overall result.
   About half of the included studies were originally RCTs, analysed as prospective cohort studies. It is uncertain whether the effects of the interventions were sufficiently taken into account in these studies. Treatment allocations were included in the multivariable models or reported to be equally distributed among fish intake groups. In all but one of these studies, no further actions were taken to account for the treatment allocations, such as stratification by treatment allocation. There was only minor heterogeneity between studies (I^2 19% in the main MA) and therefore the Committee expects it did not substantially impact the results of the studies.
   No specification on type of the fish could be made by the Committee since the

studies generally did not report on associations with different types of fish.

4. Generalisability:
   The studies used for the Committee's evaluation were performed in people with CVD and with CHD. There are no indications that the results would be different for people with CVD or CHD. This is supported by the lack of major heterogeneity between the studies included in the Committee's evaluation.
   Both men and women were included in the studies evaluated by the Committee, although in all but one study the majority was men. The study in which the majority was women (Mohan et al.[17]; PURE study; 57% women; HR 0.91 (95%CI 0.71, 1.16) for high versus low fish intake) and the study by Iestra et al.[16] that presented results for women separately (HR 1.04 (95% CI 0.57, 1.89) for high versus low fish intake) showed that the fish intake was not associated with all-cause mortality risk, which is not in line with the overall result of the studies. However, this observation is based on only two studies of which one was rather small. This limited the Committee in coming to a conclusion on whether there are indications to expect associations are different in women than men.

Cohort studies show that people with ASCVD with a relatively high consumption of fish have a lower risk of total CVD than people with a relatively low consumption. The evidence is strong. Most studies addressed intakes between 3 and 6 portions of fish per week compared to no or occasional fish consumption. These studies show that these people have a lower risk of total CVD. The evidence is strong. People who consume 2 portions per week also have a reduced total CVD risk. This evidence is limited. There is too little evidence to draw a conclusion on the association of consumption of 1 portion fish a week versus no or occasional consumption of fish.

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

1. Number of studies and cases:
   There are 5 cohort studies that addressed the association between fish consumption and total CVD in people with ASCVD. In total, there were > 500 events counted in these studies.[17,18,8] 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 estimate of 4 of these studies[17,18] showed a statistically significant reduction in the risk of total CVD with relatively high versus low fish intake, with little heterogeneity between studies (I^2 22%). A fifth' study, of Stewart et al.[8], addressed

the association between fish consumption and total CVD continuously (Mediterranean diet was the main exposure of the study) and reported a statistically significant reduction in the risk of total CVD with higher fish consumption, what is in line with these pooled results. The Committee added the study in an additional analysis in which the HR for the continuous association was converted to estimates per category (as explained in Chapter 2). This strengthened the associations but increased heterogeneity (I^2 74%). There was no heterogeneity in the direction of the association (all reported reduced risks) but rather in the size and/or strength of the association. Possibly, this is partly due to the approach used to calculate HRs per category, which likely resulted in overestimation of the precision of the association. Also, the highest intake category studied by Stewart et al. reflected substantially higher fish intakes than the other studies (11 portions per week versus 3 to 6 portions a week in the other studies). Because of this, the Committee judged the evidence for low versus high intakes as strong but did not quantify the conclusion.

Most of the studies compared intakes of 3 to 6 portions per week to no or occasional consumption of fish. The results were very similar to these of the high versus low intake comparisons (were based on the same studies), and the Committee also judged the evidence as strong but did not quantify the conclusion. The findings for intakes of 2 portions fish per week compared to no or occasional consumption of fish were not substantially different from these for 3 to 6 portions per week. However, there were too few studies included (n=4) in the evaluation of 2 portions of fish to draw a conclusion with strong evidence, and therefore the Committee judged there was limited evidence for a reduced risk. For consumption of 1 versus no or occasional fish consumption there were three studies that overall reported no association. Adding the study by Stewart et al. changed the pooled result to a reduced risk. However, due to possible overestimation of precision of the association for this study, and lack of robustness of the findings, the Committee judged there was too little evidence to draw a conclusion on the association of 1 portion a week with total CVD.

3. Considerations regarding the quality of the evidence:
   One of the studies included in the main MA did not adjust for the use of lipid-lowering and blood pressure-lowering medication.[18] Discarding this study did not substantially change the overall results.
   All but two of the included studies in the main MA (analysis b) were originally RCTs, analysed as prospective cohort studies. It is uncertain whether the effects of the RCT interventions were sufficiently taken into account in these studies. Treatment allocations were included in the multivariable models or reported to be equally distributed among fish intake groups. No further actions were taken to account for

the treatment allocations, such as stratification by treatment allocation. There was no heterogeneity between studies in the main MA (analysis b) and therefore the Committee expects it did not substantially impact the results of the studies.
No specification on type of the fish could be made by the Committee since the studies generally did not report on associations with different types of fish.

4. Generalisability:
   The studies used for the Committee's evaluation were performed in people with CVD and with CHD. There are no indications that the results would be different for people with CVD or CHD. This is supported by lack of heterogeneity between the studies included in the in the main MA (analysis b) of the Committee's evaluation. Both men and women were included in the studies evaluated by the Committee, although in all but one study the majority was men. The study in which the majority was women (Mohan et al.[17]; PURE study) did not show materially different results from the studies in which the majority was men. Based on the current evaluation, the Committee sees no reason to expect that associations would be different in men and women.

Cohort studies show that people with ASCVD with a relatively high compared to a relatively low consumption of fish have a lower risk of CVD mortality. The evidence is limited. The studies addressed intakes between 1 and 6 portions of fish per week compared to no or occasional fish consumption. These studies show that people with ASCVD who consume 2 to 6 portions a week have a lower risk of CVD mortality. The evidence is limited. There is too little evidence to draw a conclusion on the association of consumption of 1 portion fish a week versus no or occasional consumption of fish.

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion: There are 4 cohort studies that reported on the associations of fish consumption with risk of CVD mortality in people with ASCVD. This excludes a conclusion with strong evidence. The studies show that a relatively high versus low consumption of fish (tends to) associates with a reduced risk of CVD mortality. For intakes of fish of 2 to 6 portions per week compared to no or occasional fish consumption, consistent (tendencies towards) reduced risks for CVD mortality were reported in the cohort studies. However, there were too few studies to draw a quantified conclusion. For 1 portion of fish per week compared to no or occasional consumption there were too few studies to draw a conclusion since the studies tended to show there is no association with CVD mortality. According to the decision tree, at least five studies are needed in order to be able to draw such a conclusion, and therefore no conclusion could be drawn.

Cohort studies show that people with ASCVD with a relatively high compared to a relatively low consumption of fish have a lower risk of MI. The evidence is limited. Most studies addressed intakes between 1 and 6 portions of fish per week compared to no or occasional fish consumption. These studies show that people with ASCVD who consume 3 to 6 portions of fish a week have a lower risk of MI. The evidence is limited. There is too little evidence to draw a conclusion on the association of consumption of 1 and 2 portions fish a week versus no or occasional consumption of fish.

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion: There are 4 cohort studies that reported on the associations between fish consumption and MI risk in people with ASCVD. This excludes a conclusion with strong evidence. Three studies showed (tendencies toward) reduced risks of MI with a high versus low intake of fish. The study of Manger et al.[15] did not find an association of high versus low fish consumption, possibly due to the high fish intake of the population studied by Manger et al. This study was relatively small and likely does not impact the overall result of a reduced MI risk. Intakes of 3 to 6 portions of fish a week compared to no or occasional consumption of fish associated with reduced MI risk in particular. For lower intakes, there were too few studies to draw a conclusion since the studies tended to show there is no statistically significant association with MI risk. According to the decision tree, at least five studies are needed in order to be able to draw such a conclusion, and therefore no conclusion could be drawn.

There is too little evidence from cohort studies to draw conclusions on the associations of fish consumption with the risks of sudden cardiac death, stroke, total CHD and CHD 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:

Regarding sudden cardiac death: There are 3 cohort studies that reported on the associations between fish consumption and the risk of sudden cardiac death in people with ASCVD, and these showed no statistically significant associations between fish consumption and sudden cardiac death. Three studies provide too little evidence to draw conclusions of no association. Therefore, the Committee concluded there was too little evidence to draw a conclusion on the association between fish consumption and the risk of sudden cardiac death in people with ASCVD.

Regarding stroke: There are 3 cohort studies that reported on the associations between fish consumption and stroke risk in people with ASCVD. This excludes a

conclusion with strong evidence. The studies showed inconsistent results, with a pooled estimate of 2 studies showing a borderline statistically significantly increased stroke risk with consumption of 3 to 6 portions of fish and the other cohort study showing no association. It is unclear what caused this heterogeneity. At lower intakes, none of the cohort studies reported statistically significant associations. Three studies provide too little evidence to draw conclusions of no association and/or inconclusive evidence. Therefore, the Committee concluded there was too little evidence to draw a conclusion on the association between fish consumption and stroke risk in people with ASCVD.

Regarding total CHD and CHD mortality: There are 2 cohort studies that reported on the associations between fish consumption and the risk of total CHD and 3 on the risk of CHD mortality in people with ASCVD. The two studies on total CHD showed no statistically significant associations with fish consumption. Two studies provide too little evidence to draw a conclusion on the association between fish consumption and the risk of total CHD in people with ASCVD. Of the three studies on the CHD mortality outcome, one showed a statistically significant protective association with 2 portions per week, but not with less or more portions a week. The other two studies reported no associations. Three studies provide too little evidence to draw conclusions of no association and/or inconclusive evidence. Therefore, the Committee concluded there was too little evidence to draw a conclusion on the association of fish consumption with CHD mortality in people with ASCVD.

Summaries of cohort studies selected by the Committee

The study by Mohan et al.[17] is a pooled study of four cohorts that examined the association between fish consumption and health outcomes in people with established CVD and those without. Separate analyses were performed in people with a history of CVD or high risk of CVD. From this report, the Committee selected the results of 3 studies entirely performed in people with established CVD (PURE, ONTARGET and TRANCEND). The median fish consumption in the overall study population ranged from 4.2 g/week in South Asia to 468.3 g/week in Southeast Asia. Overall median fish consumption was approximately 100 g/week. Fish consumption in people with established CVD was not reported. PURE included shellfish in total fish consumption. ONTARGET/TRANCEND did not define which types of fish were included in total fish consumption.

In the PURE participants, (tendencies towards) inverse associations were found between fish consumption and the risks of major CVD, CVD mortality and MI. For sudden cardiac death, an inverse association was found with an average fish consumption of 1 portion a week (50 g/month to <175 g/week) compared to no or sporadic consumption of fish (< 50 g/month), but not with higher fish intakes. No statistically significant associations were found with all-cause mortality and stroke.

In TRANSCEND/ ONTARGET participants, fish consumption associated with (tendencies towards) reduced risks of all-cause mortality, major CVD, CVD mortality and MI. A borderline statistically significant increased risk of 25% was found for stroke in the highest (> 350 g/week) versus lowest intake group of fish (< 50 g/month), but not with lower intakes of fish. No association was found with sudden cardiac death.
The geographical regions differed within and across studies. More specifically, in the PURE study a large share of participants came from low-income countries whereas in the ONTARGET/TRANSCEND studies more than half of the study population came from high-income countries. It was reported that the associations found in the people with established CVD were not heterogeneous across different geographical regions.
Data from ONTARGET/TRANSCEND initially originated from trials in which the effect of antihypertension medication was examined. Treatment allocations were included in the multivariable adjusted model. Moreover, the associations were adjusted for total energy intake and several food groups, including fruit, vegetables, meat and dairy.
The report does not specify how long after the diagnosis of CVD people were included in the study, and at what time point in the study (and thus how long after the CVD diagnosis) fish consumption was assessed. Since the report does not explicitly mention that people with recent CVD index events were included, it is most likely that the event did not take place recently.
The PURE study used country specific validated FFQs at study enrolment. ONTARGET/ TRANSCEND used qualitative FFQs that had been validated against 4 dietary recalls and a comprehensive FFQ in Argentina, Brazil, and Colombia (unpublished data), and has been found to be applicable to different countries despite regional differences in dietary constituents. The results of validation were not reported for PURE and ONTARGET/ TRANSCEND.
Subgroup analyses by type of fish were not available for the ONTARGET/TRANSCEND and PURE studies. Of note, a fourth study, included by Mohan et al. that was not evaluated by the Committee because the study population consisted of only 60% people with ASCVD, found reduced risks of all-cause mortality, total CVD and a composite outcome for consumption of fish that are high or moderate in omega-3 fatty acids (4 to 6% statistically significant risk reductions per 5% increment). No associations were found with fish that are low in omega-3 fatty acids and shellfish.
Funders of the studies were not involved in the design, data collection, analysis, interpretation or publication of the study. Some of the authors received grants from multiple pharmacological companies (e.g., Amgen, Sanofi, Astra Zeneca, etc.). This is unlikely to have influenced the studies' findings.

The study by Barzi et al.[20] showed that consuming two or more portions of fish a week was associated with a reduced risk of all-cause mortality in Italian people who survived an MI compared to consuming no fish. At baseline, fish was consumed once a week or

more by approximately 70% of subjects, with an increasing consumption over the study duration. It was not specified whether eating shellfish was considered fish consumption. People divided over 172 different centres were included in the GISSI-Prevention trial when they recently (3 months or less) survived an MI. People who had an unfavourable short-term prognosis were excluded from the study. Dietary information was obtained at the randomisation visit of the GISSI-Prevention trial and at 6, 18 and 42 months of follow-up. Fish consumption was calculated by a cumulative average, and therefore the fish intake likely reflects the habitual intake to a large extent (outside the acute phase of the disease). However, the questionnaire used by Barzi et al. to estimate fish consumption was a very concise, non-validated questionnaire into the frequency of consumption of a selection of food items related to the Mediterranean diet. Adjustment for energy intake in the data-analyses was therefore not possible. The authors did adjust for the intake of other foods such as vegetables and olive oil. The data-analysis also accounted for the possible treatment effects of the trial by taking the treatment allocation as a confounding variable, which were EPA and DHA supplements. No subgroup analyses were performed by treatment group. However, for the main analysis, which examined a dietary score based on the consumption of multiple food groups, including fish, there were no differences in the association with all-cause mortality between treatment groups. The study included a large number of study participants and events. The median or mean follow-up period was not reported. No notable funding sources of the study were reported. Conflicts of interest of the authors were not reported.

The study by Erkkilä et al.[18] found no associations between fish consumption and different health outcomes, although, for the all-cause mortality outcome, there was a borderline statistically significant reduced risk with > 57 g/d compared to 0 g/d, and borderline significant reducing trend in risk with higher intakes. This may, among other things, be due to the relatively small number of participants and cases in the study. The study was performed in Finnish people with previously established CHD. The median time interval between hospital admission for CHD and the interview where information was obtained on fish consumption was 20 months (range: 10-48 months). In addition, the authors mentioned the participants were in a stable phase of their disease. This suggests the fish consumption reflects the habitual post-event intake. The median fish consumption was 57 g/d. Erkkilä et al. did not specify whether eating shellfish was considered as fish consumption. Fish intake, measured with food records, was correlated with proportions of EPA (r= 0.568, P <0.01) and DHA (r= 0.545, P <0.01) in serum cholesteryl esters. The report does not mention if participants used fish oil supplements or whether these supplements were taken into account for analysis. The analyses were adjusted for energy intake but not for other food groups.
No notable funding sources were reported. In addition, none of the authors reported to

have any conflicts of financial or personal interest with the financial sponsor of their research.

Manger et al.[15] found no associations of fish intake with all-cause mortality or future coronary events in Norwegian people with CHD. Neither were there associations with subtypes of fish (oily fish, lean fish, or processed fish). This may, among other things, be due to the relatively low number of cases in the study, and the relatively high intake of fish in this population. The mean fish intakes over the quartiles of fish intake ranged from 41.1 ± 16.3 g/d to 198.0 ± 63.8 g/d. The authors noted that a high methyl mercury intake is unlikely to have accounted for the lack of association since it was estimated that only <1% of the Norwegian population is at risk of exceeding the upper limit of intake.
The analyses were performed in data of the WENBIT trial, which examined the effect of homocysteine-lowering B vitamins. The different treatment groups, folic acid plus vitamin B12, vitamin B6, a combination of these or a placebo, were not included in the multivariable model for adjustment. However, it is mentioned in the report that the treatment allocation was evenly distributed across the quartiles of fish intake. The analyses were neither adjusted for energy intake nor intake of other foods.
The authors do not specify how much time before their start in the study the participants were diagnosed with CHD. The FFQ, which was used to measure fish intake, was self-administered by participants at their home and sent by mail or collected at the first follow-up after 1 month of enrolment. It is likely that participants enrolled in the study after onset of CHD (>6 months) and therefore that the fish intake assessment reflects their habitual intake.
The FFQ was validated against plasma phospholipid fatty acid concentrations in adults and older Norwegian men and women with reported correlations of 0.51 and 0.49, and the ability to classify 81% and 78% into the same or adjacent quartile, for EPA and DHA respectively. Shellfish was included in the list of fish items. The FFQ also included questions about fish oil supplement intake, but this was not included in total fish intake.
Participants were predominantly male (80.5%), therefore limiting the generalisability of the results to women. In addition, the study population had a high use of statins (~90%).
None of the authors reported a conflict of interest. The treatment capsules were provided by Pharma Inc. In addition, Pharma Inc. generated the randomisation sequence, concealed the randomisation code free of charge, and rendered a limited grant to finance the initial phase of the trial. It is not expected that results of the study were influenced by this since Pharma Inc. had no role in the design or the implementation of the trial, had no access to study data, and did not participate in the data analysis, interpretation or in the preparation, review, or approval of the manuscript.

The study by Stewart et al.[8] found a 10% risk reduction for MACE (non-fatal MI, non-fatal stroke, or mortality from a cardiovascular cause) with one category increase of fish consumption in people from 39 countries with stable CHD. The analyses were performed in data of the STABILITY trial, in which intervention with Darapladib, a specific inhibitor of lipoprotein-associated phospholipase A_2, was investigated. In the multivariable adjusted model, adjustments for the treatment groups of the initial trial were made. However, no adjustments for energy intake or other foods were made. The period of onset of CHD before participating in the trial was not defined. However, since included participants are defined as having stable CHD it can be assumed that this is outside the acute phase of the disease (6 months). The self-administered FFQ was obtained at the baseline of the study. It is likely that the assessed fish intake reflects the habitual intake, since participants were in a stable phase of CHD. Of the study subjects, 75% consumed fish once a week or more. It was not mentioned whether eating shellfish was counted under fish intake or if fish oil supplements were taken into account. Also, it was not indicated whether the FFQ was validated. At baseline, the majority of participants were taking statins and anti-hypertensive medications.
No notable funding sources or conflicts of interests were reported.

The study by Iestra et al.[16] found no association between fish consumption and risk of all-cause mortality in people with previous MI from nine different countries in Europe. This may, among other things, be due to the small number of participants and cases and the analysed categories of fish consumption (below versus above median intake). The analysis was performed in the data from the HALE project, which combined data from participants from the SENECA and FINE cohort studies. Diagnosis of MI was self-reported (SENECA) or medically confirmed (FINE).
Food consumption data were collected by trained dieticians using a validated dietary history method. The results of the validation were not described. Iestra et al. did not specify whether eating shellfish was reported as fish consumption. In addition, it was not reported when food consumption data were collected. However, given the participants were a selection from the general (elderly) population, the Committee expects that the fish consumption was assessed outside the acute phase of the MI event.
The analysis for fish consumption was not adjusted for energy intake or other dietary components, except for alcohol intake. However, fish intake was adjusted for energy intake by dividing the daily intake by the individual's total energy intake and multiplying it by the sex and study population-specific median of energy intake. Cut-off points for dietary components used for the data-analyses were based on sex-specific medians of the healthy population of the HALE project. The cut-off value was not reported. Median fish intakes of the study population were 19 g/d and 33 g/d for men and 22 g/d and 41 g/d for women, depending on whether participants originated from Northern or

Southern Europe, respectively. These may give a general indication of the cut-offs.
No notable funding sources of the study were reported. Conflicts of interest of the authors were not reported.

Trichopoulou et al.[7] found no association between fish consumption and the risk of all-cause mortality in people with a previous MI from nine different countries in Europe. The analysis was performed in data from the EPIC study. Data from participants who were 60 years or older were included in the EPIC-Elderly project. For this analysis only data from participants included in the EPIC-Elderly project who also survived a previous MI were used.
The mean fish and seafood consumption was 42.8 ± 36.0 g/d for men and 35.2 ± 34.7 g/d for women. Fish consumption was measured using food frequency questionnaires or quantitative dietary questionnaires. These questionnaires were validated in each study centre, but the results of the validation were not reported by Trichopoulou et al. The participants reported their average fish consumption of the year preceding enrolment. Since the participants were a selection from the general (elderly) population, the Committee expects fish consumption was assessed outside the acute phase of the MI event.
Fish and seafood were considered as one group, meaning shellfish was included in the fish exposure under study.
The analysis was adjusted for energy and alcohol consumption but not for other food categories.
No notable funding sources of the study were reported. Conflicts of interest of the authors were not reported.

The study of Pertiwi et al.[19] found that daily fish intakes of >20 g compared to 5 g or less were associated with an approximately 30% reduced risk of CHD mortality. At intakes >40 g/d this was not statistically significant, possibly since few participants consumed such high intakes. There were no associations between fish consumption and the risk of CVD mortality and all-cause mortality. The study was performed in over 4000 Dutch participants of the alpha-omega cohort, with a prior MI. During the first 40 months of follow-up, these people participated in a trial with omega-3 fatty acid supplementation, which had no effect on CVD and CHD mortality. Fish intake was measured with a biomarker-validated FFQ. The correlation coefficients between dietary intakes and plasma values of fish fatty acids were approximately 0.4. Fish consumption was assessed at baseline, after the occurrence of the index-event (MI). The majority of participants experienced the MI more than ~1.5 years before inclusion into the study, and therefore the Committee considered the estimated fish consumption generally is likely representative for the long-term habitual (post event) intake. The average baseline total fish consumption was 14 g/d (approximately one portion per week), of which approximately one third was oily fish.

Fish intake was adjusted for total energy intake and the data-analyses took into account relevant confounders such as age, sex, smoking, cardiovascular medication use and dietary intakes of other foods such as meat. The study had a relatively high number of participants and cases, and a long follow-up. Participants were predominantly male (79%), therefore limiting the generalisability of the results to women.

The Committee notes that relatively high intakes of fish fatty acids were also associated with an approximate 30% reduced CHD mortality risk in this study. This is in line with the results on fish intake. This association was particularly present in people in the placebo group of the original RCT (p-value for interaction 0.07). According to the authors this could suggest that people on placebo with lower EPA levels could have benefited more from fish fatty acid (and likely also fish) intake in their habitual diet.

3.3 Summary of conclusions

The Committee's conclusions regarding effects and associations of fish consumption with health outcomes in people with ASCVD are summarised in Table 5.

Table 5 Summary of conclusions regarding the effects and associations of fish consumption with health outcomes in people with ASCVD

Health outcome	Study design	Portions of fish per week	Conclusion
All-cause mortality, CHD mortality, CHD morbidity	RCTs	2 to 4 portions oily fish versus no specific advice	Too little evidence[a]
All-cause mortality	Cohort studies	High versus low	15% reduced risk Strong evidence
All-cause mortality	Cohort studies	1 versus no/occasional	No association
All-cause mortality	Cohort studies	2 and 3-6 versus no/occasional	10 to 15% reduced risk Strong evidence
CVD events (total CVD)	Cohort studies	High versus low	Reduced risk Strong evidence
CVD events (total CVD)	Cohort studies	1 versus no/occasional	Too little evidence
CVD events (total CVD)	Cohort studies	2 versus no/occasional	Reduced risk Limited evidence
CVD events (total CVD)	Cohort studies	3-6 versus no/occasional	Reduced risk Strong evidence
CVD mortality	Cohort studies	High versus low	Reduced risk Limited evidence
CVD mortality	Cohort studies	1 versus no/occasional	Too little evidence
CVD mortality	Cohort studies	2 and 3-6 versus no/occasional	Reduced risk Limited evidence
MI	Cohort studies	High versus low	Reduced risk Limited evidence
MI	Cohort studies	1 and 2 versus no/occasional	Too little evidence

MI		3-6 versus no/occasional	Reduced risk Limited evidence
Sudden cardiac death, stroke, CHD events (total CHD), CHD mortality	Cohort studies	High versus low	Too little evidence
Sudden cardiac death, stroke, CHD events (total CHD), CHD mortality	Cohort studies	1, 2, and 3-6 versus no/occasional	Too little evidence

Abbreviations: ASCVD: atherosclerotic vascular disease; CHD: coronary artery disease; CVD: cardiovascular disease; MI: myocardial infarction RCT: randomised controlled trial.

[a] The Committee judged there is one RCT of good quality regarding these outcomes and concluded that based on this single RCT there is too little research. Nevertheless, it should be noted this single study can be used as supportive evidence (proof of principle RCT) for protective associations in cohort studies.

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Annexes

Annex A Search strategy and study selection

The search strategy for MAs, SRs and pooled analyses can be found in the background document on EPA and DHA.[21] Below, the search for individual cohort studies and RCTs is presented, followed by the flow diagram for the selection of studies.

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

(Fishes [MesH] OR Fishes [TIAB] OR Fish [TIAB] OR seafood [MeSH] OR seafood [TIAB])

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 Terms] OR "Review"[Publication Type] OR "meta analysis"[Publication Type] OR "Meta-Analysis as Topic"[MeSH Terms] OR "Network Meta-Analysis"[MeSH Terms] OR "Primary Prevention"[MeSH Terms])

Limit: from 2000

Scopus

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

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

AND

TITLE-ABS(Fishes) OR TITLE-ABS(Fish) OR TITLE-ABS(seafood)

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(randomised) OR TITLE-ABS-KEY(RCT) OR TITLE-ABS-KEY(controlled*) OR TITLE-ABS-KEY(placebo) OR TITLE-ABS-KEY(“clinical trial”) OR TITLE-ABS-KEY(trial) OR TITLE-ABS-KEY(intervention)
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: from 2000

A.2 Selection of individual RCTs and cohort studies

Step 1. Identification
1521 records retrieved:

- PubMed: 587
- Scopus: 927
- Other sources: 7

401 duplicates excluded

Step 2. Screening
1120 records screened,
1086 records excluded after first selection

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

- No exposure of interest

- No outcome of interest
- Different study population
- Different study design
- Study duration too short (in case of experimental study)
- Trial without control group
  Pulication on previously included study with the same published outcomes

Step 4. Inclusion

13 records included of which one pooled cohort study of 3 cohort studies, 5 RCTs and 7 cohort studies

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

Supplementary Table B1 Summary of associations of fish consumption and health outcomes in people with atherosclerotic cardiovascular disease: cohort studies of Mohan et al.

Aspect	Mohan et al. 2021[17] (PURE)	Mohan et al. 2021[17] (ONTARGET/ TRANCEND)
Study duration	9.1 years[a]	6.2 years[a]
Primary disease	CVD	CVD
Study design	Individual cohort study	Combination 2 cohort studies (RCTs by origin)
Cohort name	PURE study	ONTARGET/TRANCEND
Exposure	Fish consumption Categorised into 1: <50 g/month; 2: 50 g/month to <175 g/week; 3: 175 to <350 g/week; 4: >350 g/week	Fish consumption Categorised into 1: <50 g/month; 2: 50 g/month to <175 g/week; 3: 175 to <350 g/week; 4: >350 g/week
Dietary assessment method	Validated FFQ	Validated FFQ
Number of participants; number of cases	7818; All-cause mortality: 1115 Major CVD (MI, stroke, congestive heart failure or sudden death): 1363 CVD mortality: NR MI: NR Stroke: NR Sudden cardiac death: NR	31,491; All-cause mortality: 3771 Major CVD (MI, stroke, congestive heart failure or sudden death): 5182 CVD mortality: 2265 MI: 1552 Stroke: 1395 Sudden cardiac death: 431
Strength of the association: HR (95%CI) per category of fish consumption[b]	ALL-CAUSE MORTALITY: Compared to <50 g/mo: 50 g/mo to <175 g/w: 0.94 (0.79, 1.11) 175 to <350 g/w: 0.92 (0.73, 1.16) >350 g/w: 0.91 (0.71, 1.16) MAJOR CVD: Compared to <50 g/mo: 50 g/mo to <175 g/w: 0.95 (0.75, 1.19) 175 to <350 g/w: 0.81 (0.57, 1.13) >350 g/w: 0.72 (0.51, 1.03) CVD MORTALITY: Compared to <50 g/mo: 50 g/mo to <175 g/w: 0.95 (0.75, 1.19)	ALL-CAUSE MORTALITY: Compared to <50 g/mo: 50 g/mo to <175 g/w: 0.92 (0.82, 1.02) 175 to <350 g/w: 0.86 (0.76, 0.98) >350 g/w: 0.81 (0.70, 0.92) MAJOR CVD: Compared to <50 g/mo: 50 g/mo to <175 g/w: 0.97 (0.88, 1.08) 175 to <350 g/w: 0.89 (0.80, 1.00) >350 g/w: 0.91 (0.81, 1.03) CVD MORTALITY: Compared to <50 g/mo: 50 g/mo to <175 g/w: 0.92 (0.80, 1.06)

	175 to <350 g/w: 0.81 (0.57, 1.13) >350 g/w: 0.72 (0.51, 1.03) MI: Compared to <50 g/mo: 50 g/mo to <175 g/w: 0.95 (0.76, 1.18) 175 to <350 g/w: 0.96 (0.71, 1.29) >350 g/w: 0.71 (0.51, 0.99) STROKE: Compared to <50 g/mo: 50 g/mo to <175 g/w: 1.00 (0.80, 1.25) 175 to <350 g/w: 0.75 (0.55, 1.03) >350 g/w: 0.91 (0.66, 1.27) SUDDEN CARDIAC DEATH: Compared to <50 g/mo: 50 g/mo to <175 g/w: 0.31 (0.11, 0.87) 175 to <350 g/w: 0.80 (0.18, 3.68) >350 g/w: 0.67 (0.02, 19.2)	175 to <350 g/w: 0.87 (0.74, 1.02) >350 g/w: 0.80 (0.67, 0.96) MI: Compared to <50 g/mo: 50 g/mo to <175 g/w: 0.86 (0.72, 1.03) 175 to <350 g/w: 0.86 (0.71, 1.05) >350 g/w: 0.86 (0.69, 1.06) STROKE: Compared to <50 g/mo: 50 g/mo to <175 g/w: 1.11 (0.91, 1.36) 175 to <350 g/w: 0.99 (0.80, 1.24) >350 g/w: 1.25 (1.00, 1.58) SUDDEN CARDIAC DEATH: Compared to <50 g/mo: 50 g/mo to <175 g/w: 1.04 (0.74, 1.46) 175 to <350 g/w: 1.05 (0.72, 1.52) >350 g/w: 0.94 (0.63, 1.42)
Study population	People with CVD; BMI: NR; medication: NR; men (42% in total study population) and women (58% in total study population); 21 countries in South Asia (36%), China (28%), Southeast Asia (1%), Africa (4%), North America or Europe (4%), Middle East (7%), South America (21%)	People with CVD; BMI: 28 ± 4.6 kg/m^2; medication: NR; men (69%) and women (31%); 40 countries in North America or Europe (55%), South America or Mexico (31%), Middle East (1%), China, Hong Kong, Taiwan or South Korea (7%), Southeast Asia (1%), Africa (2%), Oceania (5%).

Abbreviations: BMI: body mass index; CI: confidence interval; CVD: cardio vascular disease; d: day; FFQ: food frequency questionnaire; HR: hazard ratio; MI: myocardial infarction; mo: month; NR: not reported; ONTARGET: Ongoing Telmisartan Alone and in Combination With Raminipril Global End Point Trial; PURE: Prospective Urban Rural Epidemiology; RCT: randomised controlled trial; TRANSCEND: Telmisartan Randomised Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease; w: week.

[a] Value represents the median follow-up.

[b] Statistical model adjusted for the following confounders: Mohan et al. (2021): age, sex, study center, BMI, education, smoking status, physical activity, alcohol intake, urban/rural location, history of diabetes, cardiovascular disease and cancer, use of statin medication, anti-hypertension medication, fruit, vegetables, red meat, poultry, dairy, and total energy intake;

Supplementary Table B2 Summary of associations of fish consumption and health outcomes in people with atherosclerotic cardiovascular disease: cohort studies of Barzi et al. and Erkillä et al.

Aspect	Barzi et al. 2003[20]	Erkillä et al. 2003[18]
Study duration	60,008 person years	5 years[a]
Primary disease	CHD	CHD
Study design	Individual cohort study (RCT by origin)	Individual cohort study
Cohort name	GISSI-Prevenzione study	EUROASPIRE
Exposure	Fish consumption Categorised into never; 1 a week; 2 a week; >2 a week	Fish consumption Categorised into 0 g/d; below median consumption (<57 g/d); above median consumption (>57 g/d)
Dietary assessment method	Simple dietary frequency questionnaire, 6 months, 18 months and 42 months and fish intake calculated by cumulative average	Self-administered 4-d food record (3 week days and 1 weekend day)
Number of participants; number of cases	11,246 participants; All-cause mortality: 1660	415 participants; All-cause mortality: 36 Cardiovascular mortality: 21 Coronary artery disease mortality: 18 Incidence of nonfatal AMI: 21 Incidence of CABG or PTCA: 39 Incidence of stroke: 12
Strength of the association: HR or OR (95%CI) per category of fish consumption[b]	ALL-CAUSE MORTALITY: Compared to never: 1/week: 0.87 (0.75, 1.02) 2/week: 0.81 (0.69, 0.94) >2/week: 0.76 (0.62, 0.94) *P*- linear trend <0.001	Compared to 0 g/d: ALL-CAUSE MORTALITY: 1-57 g/d: 0.50 (0.20, 1,28) >57 g/d: 0.37 (0.14, 1.00) *P*- linear trend 0.06 CHD MORTALITY: 1-57 g/d: 1.59 (0.39, 6.49) >57 g/d: 1.04 (0.25, 4.31) *P*- linear trend 0.73 CHD MORTALITY OR AMI: 1-57 g/d: 1.00 (0.38, 2.66) >57 g/d: 0.49 (0.17, 1.41) *P*- linear trend 0.21

		CVD MORTALITY, AMI OR STROKE: 1-57 g/d: 0.64 (0.28, 1,47) >57 g/d: 0.45 (0.19, 1.09) *P*- linear trend 0.12 REVASCULARISATION: 1-57 g/d: 1.89 (0.68, 5.25) >57 g/d: 1.09 (0.37, 3.17) *P*- linear trend 0.23
Study population	People who survived a recent (3 months or less) MI; BMI: 26.5 ± 3.7 kg/m^2; medication: aspirin (80%), anti-platelet therapy (92%), ACE-inhibitors (47%), beta-blockers (44%); men (85%) and women (15%); Europe (Italy)	People with clinically established CHD; BMI: 28.2 ± 4.2 kg/m^2 (people who died), 28.1 ±4.0 kg/m^2 (people who survived); medication: NR; men (69%) and women (31%); Europe (Finland)

Abbreviations: ACE: angiotensin-converting enzyme; BMI: body mass index; CHD: coronary heart disease; CI: confidence interval; CVD: cardio vascular disease; d: day; EUROASPIRE: European Action on Secondary Prevention through Intervention to Reduce Events; GISSI: Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca; HR: hazard ratio; MI: myocardial infarction; NR: not reported; RCT: randomised controlled trial.

[a] Value represents the maximum follow-up.

[b] Statistical model adjusted for the following confounders: Barzi et al. (2003): age, sex, hypertension, HDL-cholesterol, diabetes, smoking, claudication, electrical instability, left ventricular dysfunction, residual myocardial ischaemia, dietary supplementation (vitamin E, n-3 PUFA and the interaction), pharmacological therapies (aspirin, beta-blockers, ACE inhibitors), consumption of fruit, raw vegetables, cooked vegetables, olive oil; Erkillä et al. (2009): sex, diagnostic category (CABG or PTCA compared with AMI or AMIS), education, serum cholesterol concentration, serum triaglycerol concentration, BMI, diabetes, energy intake.

Supplementary Table B3 Summary of associations of fish consumption and health outcomes in people with atherosclerotic cardiovascular disease: cohort studies of Manger et al. and Stewart et al.

Aspect	Manger et al. 2010[15]	Stewart et al. 2016[8]
Study duration	4.8 years[a]	3.7 years[a]
Primary disease	CHD	CHD
Study design	Individual cohort study (RCT by origin)	Individual cohort study (RCT by origin)
Cohort name	WENBIT	STABILITY trial
Exposure	Fish consumption Categorised into quartiles (mean ± SD) 1: 41.1 ± 16.3 g/d; 2: 81.4 ± 9.3 g/d; 3: 118.0 ± 12.4 g/d; 4: 198.0 ± 63.8 g/d	Fish consumption Categorised into never or rarely; once a week; several times a week; 1-2 servings a day
Dietary assessment method	Validated semi quantitative FFQ at baseline	Self-administered FFQ
Number of participants; number of cases	2412 participants; All-cause mortality: 137 Coronary event: 292	15,482; MACE[d]: 1588

	Coronary mortality: 76 AMI: 210 Stable angina pectoris that showed progression: 298	
Strength of the association: HR (95%CI) per category of fish consumption[b]	Compared to 41 g/d: ALL-CAUSE MORTALITY: 81 g/d: 0.85 (0.52, 1.37) 118 g/d: 0.97 (0.61, 1.55) 198 g/d: 0.95 (0.58, 1.55) *P*- linear trend 0.98 CORONARY EVENTS: 81 g/d: 1.08 (0.78, 1.50) 118 g/d: 1.07 (0.77, 1.48) 198 g/d: 1.04 (0.74, 1.45) *P*- linear trend 0.86 CORONARY MORTALITY: 81 g/d: 0.79 (0.42, 1.51) 118 g/d: 0.83 (0.44, 1.56) 198 g/d: 1.03 (0.54, 1.94) *P*- linear trend 0.94 AMI: 81 g/d: 1.05 (0.72, 1.53) 118 g/d: 1.01 (0.69, 1.49) 198 g/d: 0.93 (0.63, 1.40) *P*- linear trend 0.72 STABLE ANGINGA WITH PROGRESSION OF CHD: 81 g/d: 1.24 (0.89, 1.72) 118 g/d: 0.93 (0.66, 1.32) 198 g/d: 1.34 (0.97, 1.85) *P*- linear trend: 0.23	MACE[c]: Per 1 category increase: 0.90 (0.84, 0.97) *P*-linear trend <0.05
Study population	People >18 years who were undergoing coronary angiography for CHD and/or stenosis; BMI ranging from 26.6 ± 3.5 to 27.2 ± 3.9 kg/m^2 over the quartiles of fish intake; medication: acetylsalicylic acid (90%), statins (89%), beta-blockers (78%), ACE inhibitors/ ARBs (32%), calcium channel blockers (23%), loop diuretics	People ≥60 years with stable CHD[d]; BMI: 38% ≥30 kg/m^2; medication: NR; men (81%) and women (19%); 39 countries in Asia or South Africa (17%), Eastern Europe (25%), North America (26%), South America and Mexico (9%), Western Europe and Oceania (24%)

	(9%); men (80%) and women (20%); Europe (Norway)

Abbreviations: ACE: angiotensin-converting enzyme; AMI: acute myocardial infarction; ARB: angiotensin receptor blocker; BMI: body mass index; CHD: coronary heart disease; CI: confidence interval; d: day; FFQ: food frequency questionnaire; HR: hazard ratio; MACE: major adverse cardiovascular events; RCT: randomised controlled trial; STABILITY: stabilization of atherosclerotic plaque by initiation of darapladib therapy; WENBIT: Western Norway B Vitamin Intervention Trial.

[a] Value represents the median follow-up.

[b] Statistical model adjusted for the following confounders: Manger et al. (2010): age, sex, left ventricular ejection fraction (continuous), diabetes mellitus, hypertension, current smoker, acute coronary syndrome, current use of statins; Stewart et al. (2016): treatment group, age, sex, smoking, markers of disease severity (prior myocardial infarction, prior coronary revascularisation, multi-vessel disease confirmed by angiography, polyvascular disease and eGFR <60mls/min/m2), CV risk factors (history of hypertension, diabetes mellitus, HDL and LDL cholesterol, body mass index and total self-reported physical activity), geographic region, world bank country income level and education.

[c] MACE was defined as non-fatal MI, non-fatal stroke, or mortality from a CV cause.

[d] Stable CHD was defined as prior MI, prior coronary revascularisation, or multi-vessel CHD. Besides stable CHD, participants also had to meet one of the following CV risk criteria: age ≥60 years, diabetes mellitus requiring pharmacotherapy, HDL-cholesterol 1.03 mmol/L, current or previous smoker, significant renal dysfunction defined as estimated glomerular filtration rate ≥30 and 60 mL/min per 1.73 m^2 or urine albumin to creatinine ratio ≥30 mg albumin/g creatinine, or polyvascular disease defined as CHD and cerebrovascular disease or CHD and peripheral arterial disease.

Supplementary Table B4 Summary of associations of fish consumption and health outcomes in people with atherosclerotic cardiovascular disease: cohort studies of Iestra et al. and Trichopoulou et al.

Aspect	Iestra et al. 2006[16]	Trichopoulou et al. 2007[7]
Study duration	10 years[a]	6.7 years[b]
Primary disease	CHD	CHD
Study design	Individual cohort study	Individual cohort study
Cohort name	HALE project	EPIC-Elderly study
Exposure	Fish consumption Categorised into below or above energy adjusted median of the healthy study population of the HALE project; median NR	Fish and seafood consumption analysed per 35 g/d increment
Dietary assessment method	Validated dietary history method	Self- or interviewer-administered FFQ or quantitative dietary questionnaire
Number of participants; number of cases	426; All-cause mortality: 247	2671; All-cause mortality: 467
Strength of the association: HR (95%CI) per category of fish consumption[c]	ALL-CAUSE MORTALITY: 0.80 (0.70, 1.18) Subgroup analyses: Men: 0.79 (0.59, 1.06) Women: 1.04 (0.57, 1.89) Northern Europe: 0.81 (0.53, 1.13) Southern Europe: 1.20 (0.74, 1.97)	ALL-CAUSE MORTALITY: Per 35 g/d increment: 1.02 (0,92, 1.13)

Study population	People ≥70 years with a history of MI; body weight status: 21% obese; medication: NR; men (67%) and women (33%); 10 European countries (Finland, Netherlands, Denmark, Belgium, France, Switzerland, Portugal, Spain, Italy, Greece)	People ≥60 years with previous MI; BMI: NR; medication: NR; men (69%) and women (31%); 9 European countries (Denmark, France, Germany, Greece, Italy, Netherlands, Spain, Sweden, United Kingdom)

Abbreviations: BMI: body mass index; CHD: coronary heart disease; CI: confidence interval; d: day; EPIC: European Prospective Investigation into Cancer and Nutrition; FFQ: food frequency questionnaire; HALE: Healthy Ageing: a Longitudinal study in Europe; HR: hazard ratio; MI: myocardial infarction; NR: not reported;

[a] Value represents de mean follow-up

[b] Value represents the median follow-up.

[c] Statistical model adjusted for the following confounders: Iestra et al. (2006): study (SENECA/FINE), gender, age, years of education, BMI, history of diabetes, history of stroke, smoking, physical activity, alcohol consumption. Fish intake was adjusted for energy intake; Trichopoulou et al. (2007): sex, age, diabetes mellitus at baseline, previous treatment for hypertension, previous treatment for hypercholesterolemia, waist to hip ratio, BMI, educational achievement, smoking status, physical activity at work, physical activity at leisure, alcohol intake, total energy intake. Models were stratified by country.

Supplementary Table B5 Summary of associations of fish consumption and health outcomes in people with atherosclerotic cardiovascular disease: cohort study of Pertiwi et al.

Aspect	Pertiwi et al.[19]
Study duration	12 years[a]
Primary disease	CHD
Study design	Individual cohort study (RCT by origin)
Cohort name	Alpha Omega Cohort
Exposure	Fish consumption categorised into: ≤5 g/d; >5-20 g/d; >20-40 g/d; >40 g/d
Dietary assessment method	Validated FFQ
Number of participants; number of cases	4067; All-cause mortality: 1877 CVD mortality: 834 CHD mortality: 515
Strength of the association: HR (95%CI) per category of fish consumption[b]	Compared to ≤5 g/d: ALL-CAUSE MORTALITY: >5-20 g/d: 1.03 (0.92, 1.15) >20-40 g/d: 0.98 (0.84, 1.15) >40 g/d: 0.97 (0.82, 1.15) CVD mortality: >5-20 g/d: 1.04 (0.88, 1.22) >20-40 g/d: 0.91 (0.72, 1.16) >40 g/d: 0.91 (0.70, 1.18)

	CHD mortality: >5-20 g/d: 0.85 (0.70. 1.04) >20-40 g/d: 0.73 (0.54, 0.99) >40 g/d: 0.74 (0.53, 1.03)
Study population	People with previous MI; BMI: 27.7 ± 3.8 kg/m^2; men (79%) and women (21%); medication: statins (86%), antihypertensive drugs (90%), antithrombotic drugs (98%); Europe (the Netherlands)

Abbreviations: BMI: body mass index; CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; d: day; FFQ: food frequency questionnaire; HR: hazard ratio; MI: myocardial infarction; RCT: randomised controlled trial.

[a] Value represents the median follow-up.

[b] Statistical model adjusted for the following confounders: Pertiwi et al. (2021): age, sex, education level, physical activity, smoking status, alcohol intake, obesity, prevalent diabetes, cardiovascular drugs, time since myocardial infarction, and energy-adjusted intakes of meat, grains, fruits, and vegetables. Fish intake was adjusted for energy intake.

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