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ARTICLE

Food and health

Fish consumption and risk of stroke, coronary heart disease, and cardiovascular mortality in a Dutch population with low fish intake

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Abstract

Background/objectives Fish consumption of at least 1 portion/week is related to lower cardiovascular disease (CVD) risk. It is uncertain whether a less frequent intake is also beneficial and whether the type of fish matters. We investigated associations of very low intakes of total, fatty, and lean fish, compared with no fish intake, with 18-year incidences of stroke, coronary heart disease (CHD), and CVD mortality.

Methods Data were used from 34,033 participants, aged 20–70 years, of the EPIC-Netherlands cohort. Baseline (1993–1997) fish consumption was estimated using a food frequency questionnaire. We compared any fish consumption, <1 portion/week (<100 g) and ≥1 portion/week to non-fish consumption.

Results During 18 follow-up years, 753 stroke events, 2134 CHD events, and 540 CVD deaths occurred. Among the fish consumers (~92%) median intakes of total, lean, and fatty fish were 57.9, 32.9, and 10.7 g/week, respectively. Any fish consumption compared with non-consumption was not associated with incidences of stroke, CHD, MI, and CVD mortality. Furthermore, consumption of <1 portion/week of total, fatty, or lean fish was not associated with any CVD outcome, as compared with non-consumption. Consumption of ≥1 portion/week of lean fish (HR: 0.70, 95% CI: 0.57–0.86) and of fatty fish (HR: 0.63, 95% CI: 0.39–1.02) were associated with lower incidence of ischaemic stroke.

Conclusions Baseline fish consumption of <1 portion/week, regardless of the type of fish, was unrelated to incidences of stroke, CHD, and CVD mortality in this Dutch cohort. Consumption of ≥1 portion/week of fatty or of lean fish reduced the incidence of ischaemic stroke.

Introduction

Dietary guidelines [1–4] advise to consume at least one serving of fish, preferably fatty fish, per week, as scientific evidence indicates this would lower the incidence of total stroke [5, 6] and fatal coronary heart disease (CHD) [7]. In the Netherlands, however, very low intakes of fish (i.e., <1 portion/week) are common, and it is still unknown whether such amounts would also be protective against cardiovascular disease (CVD).

Only few studies investigated the associations of very low fish intake with incidences of stroke and CHD [8–12] and their findings are conflicting. Three studies showed no associations between very low fish intake and incidences of total stroke [12], mortality due to stroke [12], CHD [11], or myocardial infarction (MI) [8]. Two studies in the Dutch MORGEN cohort showed lower incidences of stroke in women only [10], and of CHD mortality [9]. However, both studies in MORGEN combined non-consumers with consumers of very low amounts of fish as the reference category, whereas it may be relevant to evaluate the very low fish consumers separately. In addition, none of the studies that addressed very low vs. no fish intake considered the type of fish consumed [8, 12].

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This study aims to investigate associations of very low intake compared with no intake of total fish, fatty fish, and lean fish with 18-year incidences of total stroke, haemorrhagic stroke, ischaemic stroke, CHD, MI, and CVD mortality in a Dutch population that typically consumes very low amounts of fish. Data were used from the European Prospective Investigation into Cancer and Nutrition-Netherlands (EPIC-NL) cohort. Because the aforementioned MORGEN cohort is one of the two arms of the EPIC-NL cohort, we partly repeated previous analyses in MORGEN [9, 10], but with the added value of a longer follow-up time, more cases, a larger sample size and of studying the non-fish consumers separately.

Methods

Study population

EPIC-NL consists of the Prospect and MORGEN cohorts that cover the Dutch contribution to EPIC, as described in detail previously [13]. Both cohorts were set up between 1993 and 1997, and merged into one cohort in 2007. All participants signed informed consent prior to study inclusion. Both cohorts complied with the Declaration of Helsinki and were approved by local medical ethics committees. Data on demographic, lifestyle, anthropometric, and biological factors were obtained at baseline [13].

For this study, participants were excluded if they withheld consent for linkage with disease and vital status registries ($n = 1304$), their vital status ($n = 417$) or cause of death ($n = 143$) was unknown, they had CVD ($n = 1470$), diabetes ($n = 681$), or cancer ($n = 1531$) at baseline, they had missing dietary data ($n = 117$), or if their reported energy intake was implausible (i.e., the bottom and top 0.5% of the energy intake to basal metabolic rate ratio distribution; $n = 315$). Finally, the analytical sample included 34,033 participants.

Dietary assessment

Habitual dietary intake within the preceding year was assessed at baseline using a semi-quantitative food frequency questionnaire (FFQ). Average intakes of energy, nutrients, and food groups were calculated using the 1996 Dutch food consumption database (digital update) [14]. The FFQ was validated against 12 monthly 24-h recalls from 121 participants. For total fish consumption, Spearman rank correlation coefficients were 0.32 for men and 0.37 for women [15].

To determine fish intake, participants were asked to specify the consumption frequency of fish, mussels, and prawns in times per day, week, month, or year. Subsequently, they indicated the consumption frequency of fish from three categories: (1) plaice, cod, fish fingers, and fried fillet of haddock (lean fish); (2) mussels and prawns (shellfish); and (3) eel, mackerel, fresh herring, herring, and canned fish (fatty fish). Total fish was defined as the sum of fatty fish, lean fish, and shellfish. Consumption of fish, other food groups, and nutrients, except for alcohol, were adjusted for total energy intake using the nutrient residual model [16].

Fish consumption was categorised in two different ways. In the first way, participants were categorised into non-fish consumers (0 g/week) and fish consumers (>0 g/week). The fish consumers were further categorised according to the consumption frequency of total fish into those consuming <1 portion/week (<100 g/week) and those consuming ≥1 portion/week (≥100 g/week) of fish. A similar categorisation according to consumption frequency was made based on fatty fish and on lean fish, separately. In the second way, we separated the fish consumers into those who consumed only fatty fish and those who consumed both fatty and lean fish. As none of the participants reported consumption of only lean fish, this group could not be distinguished. Shellfish was not analysed separately because of the very low intakes. With the second categorisation, we intended to investigate whether lean fish and fatty fish are differently related to incident CVD outcomes, and whether consuming one type of fish in addition to another type would yield different results compared to consuming only one type of fish.

Assessment of cardiovascular events

Incidences of fatal and non-fatal events were combined. Fatal events were obtained through linkage with Statistics Netherlands. Non-fatal events were obtained from a standardised computerised register of hospital discharge diagnoses of the Dutch Centre for Health Care Information. For these analyses, incident (fatal or non-fatal) CVD events were divided into stroke (I60–I66), haemorrhagic stroke (I60–I62), ischaemic stroke (I63 and I65), CHD (I20–I25, I46, and R96), MI (I21 and I22), and CVD mortality (I20–I26, I46, R96, G45, I60–I67, I69, I70–I74, and I50), according to the International Classification of Diseases, Tenth Revision (ICD-10). Follow-up was complete until 1 January 2011.

Data analyses

Pearson correlation coefficients were calculated between the energy-adjusted intakes of total, fatty, lean, and shellfish. Missing data were present on eight covariates, ranging from 0.05% (BMI) to 2.93% (HDL cholesterol) and handled using multiple imputation [17, 18] (Supplemental Table

Table 1 Baseline characteristics of the non-fish consumers and fish consumers in the EPIC-NL cohort

	Categories of total fish consumption							
	Median (5th–95th percentiles) intake of total fish (g/wk)							
	No consumption		Any consumption		<1 portion/wk[a]		≥1 portion/wk	
			57.9	(7.0–207.1)	36.6	(5.6–92.8)	130.1	(102.9–313.1)
No. of participants	2593		31,440		22,609		8831	
Male, %	27		25		29		17	
Age, y	48.3	±13.7[b]	48.7	±11.8	47.6	±12.0	51.4	±10.9
Physically active, %	41		42		43		41	
Current smoker, %	30		30		31		29	
High education level, %	11		22		21		23	
Body mass index, kg/m^2	25.8	±4.1	25.6	±3.9	25.5	±3.9	25.7	±4.0
Waist circumference, cm	85.7	±11.5	84.9	±11.3	85.0	±11.4	84.6	±11.2
Systolic blood pressure, mmHg	126.8	±19.5	125.7	±18.6	125.1	±18.2	127.1	±19.5
Total to HDL cholesterol ratio	4.1	(3.3–5.2)[c]	4.0	(3.2–5.0)	4.0	(3.2–5.0)	4.0	(3.2–5.0)
Dietary intake[d]								
Total energy, kcal/d	1907	(1571–2407)	1971	(1643–2388)	2036	(1690–2483)	1825	(1553–2156)
Fatty fish, g/wk	–	–	10.7	(4.7–24.2)	7.2	(3.3–15.7)	28.7	(13.6–48.6)
Lean fish, g/wk	–	–	32.9	(13.6–66.4)	21.4	(9.7–38.1)	93.7	(70.5–127.1)
Shellfish, g/wk	–	–	4.8	(2.1–11.3)	3.3	(1.5–7.9)	11.6	(5.2–21.0)
EPA, mg/d	–	–	34.7	(15.0–62.9)	21.5	(11.1–38.8)	79.6	(62.9–103.9)
DHA, mg/d	11.4	(7.1–16.5)	78.8	(41.7–132.5)	55.6	(34.8–85.4)	160.8	(138.8–199.2)
ALA, mg/d	874	(692–1130)	911	(741–1132)	909	(742–1127)	915	(740–1145)
Alcohol, g/d	1.4	(0.0–9.2)	5.7	(0.9–16.4)	5.5	(0.9–16.1)	6.1	(1.0–17.4)
Fruit, g/d	245	±170	261	±1661	251	±163	286	±169
Vegetables, g/d	130	±57	138	±541	135	±52	147	±57
Saturated fatty acids, g/d	33.4	±6.2	32.6	±5.8	33.0	±5.7	31.8	±6.0
Trans fatty acids, g/d	3.1	±1.2	2.9	±1.1	2.9	±1.1	2.7	±1.0
Fibre, g/d	23.8	±5.2	23.3	±4.7	23.3	±4.8	23.5	±4.7

ALA α-linolenic acid, *DHA* docosahexaenoic acid, *EPA* eicosapentaenoic acid, *EPIC-NL* European Prospective Investigation into Cancer and Nutrition-Netherlands, *g* grams, *HDL* high-density lipoprotein, *kg* kilogram, *mg* milligram

[a] One portion equals 100 g

[b] Data are presented as mean ± standard deviation (all such values)

[c] Data are presented as median with interquartile range (all such values)

[d] All nutrients and foods were adjusted for total energy intake, except for alcohol intake

S1). More specifically, 10 imputed datasets were constructed by fully conditional specification (Markov chain Mont Carlo method). Reported results were based on pooled values using Rubin's rule.

Cox proportional hazards models, stratified by cohort, were used to examine associations of baseline fish consumption with incidences of CVD outcomes. In all analyses, the non-fish consumers served as the reference category. Follow-up time was calculated as the time between study entrance and the occurrence of a CVD event, non-CVD death, loss to follow-up, or the end of the follow-up period (31 December 2010), whichever came first.

Two sequential Cox models were built to adjust for potential confounding. Model 1 was adjusted for age (continuous), sex, total energy intake (continuous), physical activity (inactive, moderately inactive, moderately active, active [19]), smoking status (current, former, never), education level (low (primary education up to finishing intermediate vocational education), medium (higher general secondary education), and high (higher vocational education and university)), BMI (continuous), and alcohol intake (0, 0.1–6.0, 6.1–12.0, 12.1–24.0, and >24 g/d of ethanol for women and 0, 0.1–6.0, 6.1–12.0, 12.1–24.0, 24.1–60.0, and >60 g/d of ethanol for men [20]). Model 2 was additionally adjusted for energy-adjusted intakes of saturated and trans-fatty acids, fruit, vegetables, and dietary fibre (all continuous). Fatty fish and lean fish were not mutually adjusted for because of the high correlation between those fish types.

Table 2 Fish consumption of the fish consumers in the EPIC-NL cohort, according to the types of fish

	Categories of fatty fish consumption				Categories of lean fish consumption			
	<1 portion/wk[a]		≥1 portion/wk		<1 portion/wk		≥1 portion/wk	
Total fish, g/wk	56.7	(7.0–180.8)[b]	314.5	(133.1–765.5)	50.4	(7.7–125.5)	163.5	(122.6–414.3)
Fatty fish, g/wk	10.5	(1.2–54.1)	131.1	(102.0–298.6)	9.8	(1.2–49.4)	8.2	(21.7–49.4)
Lean fish, g/wk	32.4	(2.5–136.5)	153.0	(19.3–462.5)	28.0	(3.1–85.8)	133.0	(102.6–300.2)

EPIC-NL European Prospective Investigation into Cancer and Nutrition-Netherlands, *g* grams

[a] One portion equals 100 g

[b] Data are presented as median (5th–95th percentiles) (all such values)

The proportional hazards assumption was examined by calculating Schoenfeld residuals and visual examination of log–log plots.

Sensitivity analyses

Six sensitivity analyses were performed. First, because differences between studies exist in whether shellfish is included in the definition of total fish intake, we additionally categorised the fish consumers according to the consumption frequency of total fish excluding shellfish, i.e., the sum of fatty fish and lean fish. Second, we tested whether hypertension and total to HDL cholesterol ratio, common cardiovascular risk factors, changed the association between fish consumption and CVD incidence by adding those variables to the final model (Model 2). We did not include them in the main analysis, because they may also be considered mediators [21, 22]. Third, we excluded potential energy misreporters based on the cut-offs proposed by Goldberg [23]. Fourth, to minimise the possibility of reverse causation, we repeated the analyses after exclusion of the first 2 years of follow-up. Fifth, we performed an analysis in which we used only the first 8 years of follow-up to get better understanding of the influence of the length of follow-up on the association between fish intake and long-term incidence of CVD. Last, we performed a competing risks analysis by using the subdistribution hazard model proposed by Fine and Gray [24], in which we considered death due to causes other than the CVD event of interest as the competitor. Analyses were performed using SPSS Statistics version 21 (IBM, Armonk, NY, USA) and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Of the 34,033 participants, 2593 (7.6%) reported not to consume any fish. Median (IQR) total fish intake of the fish consumers ($n = 31,440$) was 57.9 (25.7–105.9) g/week, of which ~25% was fatty fish and ~64% was lean fish (Table 1). Of the fish consumers, 71.9% consumed <1 portion of fish per week and 28.1% consumed ≥1 portion/week. Median (IQR) fish consumption according to the type and frequency of fish consumption is shown in Table 2.

On average, fish consumers were higher educated and had higher intakes of alcohol, fruit, and vegetables, compared with non-fish consumers (Table 1). Compared with participants who consumed <1 portion/week, participants who consumed ≥1 portion/week were more often women and slightly older. Baseline characteristics of fish consumers grouped according to the type of fish are shown in Supplemental Table S2. Pearson correlation coefficients between types of fish are shown in Supplemental Table S3.

Total fish consumption and incident CVD

During the 18 follow-up years (median:15.1 years), 753 stroke events, 2134 CHD events, and 540 deaths due to a cardiovascular event were reported. After adjustment for confounders, a non-significantly lower incidence of total stroke was observed in fish consumers compared with non-fish consumers (HR: 0.93, 95% CI: 0.82–1.05) (Table 3). We observed similar HRs in those who consumed <1 portion/week of total fish and in those who consumed ≥1 portion/week, compared with non-consumers. The findings were similar for haemorrhagic and ischaemic stroke. Total fish consumption was not associated with incidences of CHD, MI, and CVD mortality, regardless of the consumption frequency.

Fatty fish and lean fish consumption and incident CVD

Participants who consumed ≥1 portion/week of fatty fish had a lower incidence of total stroke (HR: 0.64, 95% CI: 0.45–0.92) and a non-significantly lower incidence of ischaemic stroke (HR: 0.63, 95% CI: 0.39–1.02), compared with non-fish consumers (Table 4). Similarly, consumers of ≥1 portion/week of lean fish had a significantly lower incidence of ischaemic stroke (HR: 0.70, 95% CI: 0.57–0.86), compared with non-fish consumers. Portions of lean fish were not associated with total stroke incidence. Also, portions of fatty fish or of lean fish were unrelated to incidences of haemorrhagic stroke, CHD, MI, or CVD mortality.

Table 3 Associations of portions of total fish consumption with incidences of total stroke, haemorrhagic stroke, ischaemic stroke, coronary heart disease, myocardial infarction, and cardiovascular mortality in the EPIC-NL cohort

	Categories of total fish consumption			
	No consumption HR	Any consumption HR (95% CI)	<1 portion/wk[a] HR (95% CI)	≥1 portion/wk HR (95% CI)
No. of participants	2593	31,440	22,609	8831
Total stroke				
Cases	69	684	470	214
Model 1[b]	1.00	0.92 (0.81–1.05)	0.93 (0.82–1.06)	0.91 (0.79–1.04)
Model 2[c]	1.00	0.93 (0.82–1.05)	0.93 (0.82–1.06)	0.91 (0.79–1.05)
Haemorrhagic stroke				
Cases	19	201	144	57
Model 1	1.00	0.91 (0.71–1.16)	0.96 (0.75–1.22)	0.80 (0.61–1.04)
Model 2	1.00	0.90 (0.71–1.15)	0.95 (0.74–1.22)	0.79 (0.60–1.03)
Ischaemic stroke				
Cases	39	374	260	114
Model 1	1.00	0.89 (0.75–1.06)	0.91 (0.77–1.09)	0.84 (0.63–1.13)
Model 2	1.00	0.91 (0.76–1.07)	0.92 (0.77–1.10)	0.87 (0.72–1.05)
Coronary heart disease				
Cases	178	1956	1388	568
Model 1	1.00	1.03 (0.96–1.12)	1.04 (0.96–1.12)	1.04 (0.95–1.13)
Model 2	1.00	1.03 (0.95–1.11)	1.03 (0.95–1.12)	1.03 (0.94–1.12)
Myocardial infarction				
Cases	62	631	459	172
Model 1	1.00	1.00 (0.87–1.14)	1.02 (0.89–1.17)	0.96 (0.83–1.11)
Model 2	1.00	1.00 (0.88–1.15)	1.02 (0.89–1.17)	0.97 (0.83–1.13)
Cardiovascular mortality				
Cases	54	486	339	147
Model 1	1.00	0.94 (0.82–1.09)	0.96 (0.83–1.11)	0.91 (0.67–1.24)
Model 2	1.00	0.96 (0.83–1.11)	0.97 (0.83–1.12)	0.94 (0.80–1.10)

BMI body mass index, *CI* confidence interval, *EPIC-NL* European Prospective Investigation into Cancer and Nutrition-Netherlands, *g* gram, *HR* hazard ratio

[a] One portion equals 100 g

[b] Model 1 is adjusted for age, sex, physical activity, smoking status, education level, BMI, alcohol intake, and total energy intake

[c] Model 2 is Model 1 and additionally adjusted for intakes of saturated fatty acids, trans fatty acids, fruit, vegetables, and dietary fibre

Consumption of only fatty fish and of both fatty and lean fish were not associated with incidences of total or subtypes of stroke, compared with non-fish consumption (Table 5). Consumption of only fatty fish was associated with lower incidences of CHD (HR: 0.82, 95% CI: 0.67–0.99), MI (HR: 0.51, 95% CI: 0.33–0.78), and CVD mortality (HR: 0.39, 95% CI: 0.25–0.63), compared with non-fish consumption, but consumption of both fatty and lean fish was not.

Sensitivity analyses

The results of the sensitivity analyses were not substantial different from the main analyses, except for the following: a lower incidence of ischaemic stroke was observed for consumption of ≥1 portion/week of total fish that excluded shellfish (HR: 0.79, 95% CI: 0.65–0.97), but not for consumption of <1 portion/week (HR: 0.94, 95% CI: 0.79–1.12), compared with non-fish consumption (Supplemental Table S4). In general, including only the first 8 follow-up years yielded stronger associations, with inverse associations for stroke outcomes. For incidences of CHD and MI, the original analyses already tended to point towards harmful associations, and those associations now became stronger and statistically significant. The results of the competing risks analyses showed, for all associations, no difference in the HRs, but wider CIs, leaving no significant associations (Supplemental Tables S4 and S5).

Table 4 Associations of portions of fatty fish consumption and of lean fish consumption with incidences of total stroke, haemorrhagic stroke, ischaemic stroke, coronary heart disease, myocardial infarction, and cardiovascular mortality in the EPIC-NL cohort

	Categories of fatty fish consumption					Categories of lean fish consumption				
	No consumption	<1 portion/wk[a]		≥1 portion/wk		No consumption	<1 portion/wk		≥1 portion/wk	
	HR	HR	(95% CI)	HR	(95% CI)	HR	HR	(95% CI)	HR	(95% CI)
No. of participants	2593	30,966		474		3188	26,956		3889	
Total stroke										
Cases	69	675		9		85	569		99	
Model 1[b]	1.00	0.93	(0.82–1.05)	0.65	(0.45–0.92)	1.00	0.96	(0.86–1.08)	0.91	(0.78–1.05)
Model 2[c]	1.00	0.93	(0.82–1.06)	0.64	(0.45–0.92)	1.00	0.97	(0.86–1.09)	0.92	(0.79–1.07)
Haemorrhagic stroke										
Cases	19	197		4		23	165		32	
Model 1	1.00	0.90	(0.71–1.15)	0.98	(0.57–1.71)	1.00	0.96	(0.77–1.21)	1.04	(0.79–1.37)
Model 2	1.00	0.90	(0.71–1.15)	0.96	(0.55–1.68)	1.00	0.96	(0.77–1.20)	1.04	(0.78–1.37)
Ischaemic stroke										
Cases	39	369		5		51	317		45	
Model 1	1.00	0.90	(0.76–1.06)	0.62	(0.39–1.01)	1.00	0.91	(0.78–1.05)	0.68	(0.55–0.84)
Model 2	1.00	0.91	(0.77–1.08)	0.63	(0.39–1.02)	1.00	0.91	(0.78–1.07)	0.70	(0.57–0.86)
Coronary heart disease										
Cases	178	1920		36		210	1682		242	
Model 1	1.00	1.03	(0.96–1.12)	1.09	(0.91–1.31)	1.00	1.09	(1.02–1.18)	0.98	(0.89–1.08)
Model 2	1.00	1.03	(0.95–1.12)	1.08	(0.90–1.30)	1.00	1.09	(1.01–1.17)	0.97	(0.88–1.07)
Myocardial infarction										
Cases	62	618		13		68	552		73	
Model 1	1.00	1.00	(0.87–1.14)	1.11	(0.82–1.51)	1.00	1.12	(0.99–1.28)	0.96	(0.81–1.13)
Model 2	1.00	1.00	(0.88–1.15)	1.12	(0.82–1.52)	1.00	1.13	(0.99–1.28)	0.97	(0.82–1.15)
Cardiovascular mortality										
Cases	54	477		9		59	406		75	
Model 1	1.00	0.95	(0.82–1.09)	0.88	(0.61–1.26)	1.00	1.08	(0.94–1.25)	1.09	(0.84–1.43)
Model 2	1.00	0.96	(0.83–1.11)	0.88	(0.61–1.27)	1.00	1.10	(0.95–1.26)	1.13	(0.94–1.35)

BMI body mass index, *CI* confidence interval, *EPIC-NL* European Prospective Investigation into Cancer and Nutrition-Netherlands, *g* gram, *HR* hazard ratio

[a] One portion equals 100 g

[b] Model 1 is adjusted for age, sex, physical activity, smoking status, education level, BMI, alcohol intake, and total energy intake

[c] Model 2 is Model 1 and additionally adjusted for intakes of saturated fatty acids, trans fatty acids, fruit, vegetables, and dietary fibre

Discussion

In the present prospective cohort study, 7.6% of the 34,033 Dutch adults consumed no fish and 66.4% consumed <1 portion/week. Fish consumption of <1 portion/week was unrelated to incidences of stroke, CHD, and CVD mortality, compared with non-fish consumption. Consumption of ≥1 portion/week of fatty fish or lean fish was associated with a lower incidence of ischaemic stroke. Relative to non-fish consumption, consumption of only fatty fish, but not of both fatty and lean fish, was associated with lower incidences of CHD, MI, and CVD mortality.

The strengths of this study include its long follow-up period, large sample size, and high number of CVD events. This study has some potential limitations. First, the relative validity of the FFQ for fish consumption was low ($r = 0.32$ for men; 0.37 for women) [15]. However, any subject misclassification is expected to be non-differential, since all study participants were free of chronic diseases at baseline. Therefore, this may only have attenuated the observed associations [25]. Second, fish intake was assessed at baseline only, so any changes in fish consumption during follow-up could not be taken into account, and this may have attenuated our findings. Third, the categorisation of fish intake has possibly induced loss of information and may have reduced our ability to find associations. However, we decided to analyse fish intake in categories as this was most appropriate to answer the research question. Fourth,

Table 5 Associations of consumption of types of fish with incidences of total stroke, haemorrhagic stroke, ischaemic stroke, coronary heart disease, myocardial infarction, and cardiovascular mortality in the EPIC-NL cohort

	Categories of fish consumption		
	No consumption	Consumption of only fatty fish	Consumption of fatty and lean fish
	HR	HR (95% CI)	HR (95% CI)
No. of participants	2593	595	30,845
Total stroke			
Cases	69	16	668
Model 1[a]	1.00	0.85 (0.65–1.13)	0.92 (0.81–1.05)
Model 2[b]	1.00	0.86 (0.65–1.14)	0.93 (0.82–1.06)
Haemorrhagic stroke			
Cases	19	4	197
Model 1	1.00	0.71 (0.41–1.24)	0.91 (0.71–1.16)
Model 2	1.00	0.71 (0.41–1.24)	0.91 (0.71–1.16)
Ischaemic stroke			
Cases	39	12	362
Model 1	1.00	1.10 (0.79–1.54)	0.88 (0.75–1.05)
Model 2	1.00	1.11 (0.80–1.56)	0.90 (0.76–1.07)
Coronary heart disease			
Cases	178	32	1924
Model 1	1.00	0.82 (0.67–0.99)	1.04 (0.96–1.13)
Model 2	1.00	0.82 (0.67–0.99)	1.04 (0.96–1.12)
Myocardial infarction			
Cases	62	6	625
Model 1	1.00	0.51 (0.33–0.78)	1.01 (0.88–1.16)
Model 2	1.00	0.51 (0.33–0.78)	1.02 (0.89–1.16)
Cardiovascular mortality			
Cases	54	5	481
Model 1	1.00	0.39 (0.25–0.63)	0.96 (0.83–1.11)
Model 2	1.00	0.39 (0.25–0.63)	0.97 (0.84–1.13)

BMI body mass index, *CI* confidence interval, *EPIC-NL* European Prospective Investigation into Cancer and Nutrition-Netherlands, *g* gram, *HR* hazard ratio

[a] Model 1 is adjusted for age, sex, physical activity, smoking status, education level, BMI, alcohol intake, and total energy intake

[b] Model 2 is Model 1 and additionally adjusted for intakes of saturated fatty acids, trans fatty acids, fruit, vegetables, and dietary fibre

we defined energy misreporters based on energy intake and the Schofield equations, using age, sex, and weight as input variables, and did not take into account the participant's physical activity level [26]. Fifth, data on the use of fish oil supplements was not available. We expect, however, that fish oil supplements were not frequently used by our study population based on previous (1992) [27] and more recent (2007–2010) [28] national food consumption data. Last, we were unable to adjust for other potential known but unmeasured (e.g., atrial fibrillation) and unknown confounders, and can therefore not rule out the possibility of residual confounding.

In the present study, consumption of ≥1 portion/week of total fish, when calculated as the sum of fatty fish and lean fish, compared with non-fish consumption, was associated with a 21% lower incidence of ischaemic stroke. Despite differences between studies in the reference category used, this finding is essentially in line with two meta-analyses [5, 6] and a previous analysis in the MORGEN cohort [10]. However, our finding differs from four studies in other European cohorts [29–32] that showed no associations. Our choice to include solely non-fish consumers in the reference category could explain this difference. It is conceivable that non-fish consumers dislike fish or have a fish allergy, and have not become fish consumers during follow-up [33]. Therefore, fish intake of our reference group was likely more stable during follow-up than the frequently used reference groups that also include participants with very low fish intakes [29, 31, 32].

Our study supports, at least for ischaemic stroke, the recommendation of the Dutch Health Council to consume ≥1 portion/week of fish to reduce stroke risk [3]. From our study, we cannot confirm that, besides the consumption frequency, the type of fish matters with regard to ischaemic stroke incidence. The fact that the associations of lean fish and of fatty fish with ischaemic stroke were of similar magnitude indicate that the associations of fatty fish and of lean fish with ischaemic stroke risk are independent of one another and may have an additive effect when consumed simultaneously. Also, as our study population predominantly ate lean fish, the observation of a lower incidence of ischaemic stroke for ≥1 portion/week of total fish may be mostly attributable to lean fish. In line with that suggestion is the lower incidence of ischaemic stroke for the consumption of lean fish, but not (salted) fatty fish, observed in a Swedish cohort [34], although this was not observed in a Spanish population [29] with a higher fish intake than in the Swedish and our Dutch cohort. Furthermore, consumption of shellfish seems unrelated to ischaemic stroke risk, because ischaemic stroke risk was associated with consumption of ≥1 portion/week of total fish when it excluded shellfish, but not when it included shellfish. Given that the HRs remain similar for all associations examined in the competing risks analyses, we conclude that the presence of competing risks likely did not affect our findings. However, we should be careful with drawing this conclusion because of the instability of the competing risk results.

The null association between total fish consumption and incident CHD is in contrast to the findings of a meta-analysis [35], in which fish consumption of <2 portions/week compared with no to very low fish consumption was associated with lower CHD risk. Fish intake in our population was potentially too low to detect an association. To illustrate, the cut-off for one portion size in that meta-analysis was higher (114 g) than in our study (100 g). In addition, a recent study in an Italian cohort [36] showed that fish consumption of >4 times/week, but not 2–4 times/week, compared with 0–2 times/week, was associated with a lower CHD incidence. Nevertheless, regarding incident MI, our findings are in line with previous studies performed in Europe [9, 31, 37] and a meta-analysis [38]. In the latter, a lower incidence of non-fatal MI was observed for fish intakes of ≥5 portions/week, and not for an intake comparable to the intake in our cohort [38].

Finally, lower incidences of CHD, MI, and CVD mortality were observed for consumption of only fatty fish—referring to only 1.7% of our cohort—compared with non-fish consumption, but not with total fish consumption. Although these findings are in line with previous studies (despite not all [39]), they need to be interpreted cautiously because of the very low amounts of fatty fish consumed and the inconsistency regarding the results of consumption frequencies of fatty fish. So, the associations we observed might be due to chance.

In conclusion, in this cohort of Dutch middle-aged adults, only 25.9% of the participants met the recommendation to consume fish at least once per week. Baseline fish consumption of <1 portion/week was unrelated to 18-year incidence of CVD. However, fish intake of ≥1 portion/week was associated with a lower incidence of ischaemic stroke, which supports the recommendation for fish consumption of the Dutch dietary guidelines [3]. Although this association was observed for intakes of fatty fish as well as lean fish, it is unclear whether the association only depends on the portion size or also on the type of fish. The associations of fish subtypes and incident CVD outcomes needs further investigation in other populations with more distinct differences in types of fish.

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Author contributions LMH, JP, YTvdS, and IS contributed to the design of the study. LMH and JP were responsible for the statistical analyses and drafted the manuscript. All authors were involved in the interpretation of the data, critically revised the manuscript, and gave final approval.

Compliance with ethical standards

Conflict of interest JP is financially supported by a restricted grant from Unilever R&D, Vlaardingen, the Netherlands. IS and YTvdS report grants from Unilever R&D, Vlaardingen, the Netherlands, outside the submitted work. The remaining authors declare that they have no conflict of interest.

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