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Fish intake, mercury, long-chain *n*-3 polyunsaturated fatty acids and risk of stroke in northern Sweden

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Results of previous studies on fish intake and stroke risk have been inconclusive. Different stroke types have often not been separated. Our aim was to elucidate whether intake of fish, Hg or the sum of proportions of fatty acids EPA (20 : 5*n*-3) and DHA (22 : 6*n*-3) influence the risk of haemorrhagic or ischaemic stroke. Within a population-based cohort from a community intervention programme, 369 stroke cases and 738 matched controls were identified and included in the present nested case–control study. Information on fish intake had been recorded at recruitment, i.e. before diagnosis. Hg levels were determined in erythrocyte membranes, also collected at recruitment, and the relative content of fatty acids was measured in erythrocyte membranes or plasma phospholipids. The results showed that in women there was a non-significant decrease in stroke risk with increasing fish intake (OR 0·90 (95 % CI 0·73, 1·11) per meal per week). The risk in women differed significantly ($P=0·03$) from that in men, in whom the OR for stroke rose with increasing fish intake (OR 1·24 (95 % CI 1·01, 1·51) per meal per week). The corresponding risk in men for Hg was 0·99 (95 % CI 0·93, 1·06), and for the sum of proportions of EPA and DHA 1·08 (95 % CI 0·92, 1·28). We conclude that the relationship between stroke risk and fish intake seems to be different in men and women. Increased levels of EPA and DHA do not decrease the risk for stroke and there is no association between stroke risk and Hg at these low levels.

Fish intake: Stroke: Methyl mercury: Eicosapentaenoic acid: Docosahexaenoic acid

Fish consumption has been reported to have a protective effect against stroke, although studies have not been consistent[1,2]. A possible explanation of the inconsistency could be that fish contains both protective and noxious agents. Examples of such agents are the long-chain fatty acids 20 : 5*n*-3 (EPA) and 22 : 6*n*-3 (DHA), believed to be beneficial, and Hg, associated with the progression of atherosclerosis in carotid arteries and a potential cause of stroke[3].

The risk pattern may vary in different types of stroke. Further, there may be differences between men and women[4].

In the present study, we aim to investigate whether the risk of ischaemic or haemorrhagic stroke is associated with fish intake in men and women, and whether Hg or EPA plus DHA affects the risk of stroke.

Materials and method

Study population

The study population was a community intervention programme on CVD and diabetes (Västerbotten Intervention Programme) and the WHO Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) study in Northern Sweden[5,6]. Participation rates were 59 and 77 %, respectively. A study on differences between participants and non-participants indicates that selection bias was small[7]. Up to 20 September 2000, approximately 74 000 unique subjects had been screened. Venous blood was sampled; erythrocytes, serum and plasma were separated and stored in a biobank at −80°C. Health-screening information was stored in a database.

End points

From 1 January 1985 to 20 September 2000, a total of 388 first-ever stroke cases fulfilling the inclusion criteria[6] were identified by the Northern Sweden MONICA incidence registry. The diagnosis of stroke was according to WHO MONICA criteria[8]. The WHO criteria excluded all transient ischaemic attacks, subdural haemorrhages and acute strokes with concomitant brain tumour or severe blood disease. Stroke subtypes were divided into intracerebral haemorrhage, cerebral infarction and unspecified stroke. Haemorrhagic stroke was diagnosed through a positive finding on computerised

Abbreviations: AMI, acute myocardial infarction; MONICA, Multinational Monitoring of Trends and Determinants in Cardiovascular Disease.

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tomography scan and/or autopsy, and in cerebral infarction no sign of haemorrhage on computerised tomography scan or autopsy was allowed. Unspecified stroke had neither computerised tomography scan nor autopsy performed. Cases diagnosed as subarachnoid haemorrhage were excluded since they were few and subarachnoid haemorrhage has another aetiology than intracerebral haemorrhage. Two controls for each case, matched for sex, age (±2 years), date of health survey (±1 year) and residential area, were randomly selected from the same health surveys. Subjects were excluded if they had been registered for a previous acute myocardial infarction (AMI) or stroke according to the MONICA registry or for cancer according to the Swedish National Cancer Registry. Controls were excluded if they had died or if they had moved out of the region before the event date of the matched case. We also excluded nineteen triplets, in which the case or both controls were lacking information on fish intake, Hg and fatty acids, leaving 302 ischaemic, sixty haemorrhagic and seven unspecified stroke cases, and 738 referents. The study was approved by the Research Ethics Committee of Umeå University.

Baseline examination

Based on the questionnaire of the health screening, smoking habits were classified into daily smoking or non-smoking (including previous and occasional smoking). BMI was calculated as weight (kg)/height (m^2). Blood pressure was measured twice at the same occasion and the mean value was recorded. Hypertension was defined as systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥95 mmHg, or reported use of anti-hypertensive medication during the previous 14 d. To evaluate the effect of the choice of blood pressure cut-off limit, we also performed analyses with hypertension defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, or reported use of anti-hypertensive medication during the previous 14 d. Diabetes diagnosis was obtained from the questionnaire. Total cholesterol was measured in serum sampled after >4 h fasting.

Fish intake

Average intake over the last year of fatty and lean fish was acquired from a FFQ. The questions asked were: 'How often do you eat lean fish (for example, perch, cod)?'; 'How often do you eat fatty fish (for example, herring, lavaret, salmon)?'; 'How often do you eat salty fish (salt herring)?'. As salt herring is a fatty fish, we assumed that the respondents had included that also in their answer on fatty fish, but for those who reported a more frequent intake of salty fish than of fatty fish (forty-nine subjects out of the total 1048), the estimation of salty fish intake was used as intake of fatty fish. Before statistical analysis the answers were transformed to meals/week of fatty, lean and total fish. The transformations of frequencies to meals/week made were: never = 0, a few times per year = 0·05, one to three times per month = 0·50, once per week = 1·00, two to three times per week = 2·50, four to six times per week = 5·00, once per d = 7·00, two to three times per d = 17·5 and four times per d or more = 28·0. Intake of total fish was also consolidated into five categories; less than once per month, once per month to less than once per week, one to two meals per week, more than twice per week to three meals per week, and more than three meals per week. The latter division in categories is only used in the figures. In Tables and text, OR is calculated per meal per week.

Determination of fatty acid composition

Fatty acids were determined by GLC after separation of lipids by TLC and transmethylation[9] and expressed as percentage of all fatty acids analysed (Unit for Clinical Nutrition Research, Department of Public Health and Caring Sciences, Uppsala University, Sweden). The CV of fatty acids measured in plasma phospholipids with this method have previously been measured to <1–5·5 %[10]. The fatty acids were identified, by comparing the retention time of each peak with the Nu Check Prep standards (Nu Check Prep, Elysian, MN, USA) of fatty acid methyl esters. The purity of these standards is greater than 99 %[11].

Fatty acids were determined by measuring plasma phospholipids in the first 113 cases and their controls. In contrast, in the subsequent 256 cases and controls we used erythrocyte membranes.

Mercury determination

Determination of total Hg was made in duplicate in acid-digested erythrocytes by cold vapour atomic fluorescence spectrometry[12] (Department of Occupational and Environmental Medicine, Lund University Hospital, Sweden). The limit of detection was 0·15 μg/l. The method imprecision, calculated as the CV for duplicate measurements, was 4·0 %. The analytical accuracy was checked using Seronorm (Nycomed Pharma, Oslo, Norway: 2·2 (SD 0·20) and 13 (SD 0·58) μg/l *v.* recommended 3·0 and 14 μg/l, respectively) and at Centre de Toxicologie du Quebec, Canada (1·9 (SD 0·09) and 9·2 (SD 0·30) μg/l *v.* certified 2·0 and 9·4 μg/l, respectively).

Statistics

The effect of each potential risk factor was first examined by univariate conditional logistic regression based on the matched case–control sets[13,14]. In the initial univariate analyses, the potential risk factors were not transformed or categorised (if not originally categorical). We then selected candidate risk factors for the multivariate analyses based on the results from the univariate analyses; each potential risk factor with a *P* value from the Wald or likelihood-ratio tests[14] less than 0·25 was selected[13]. A candidate risk factor may act as an independent risk factor, confounder or effect modifier in a multivariate setting. In order to proceed to the multivariate modelling, we analysed Spearman's correlations[15] between the candidate risk factors. Finally, to obtain the most importantly influential factors among the candidate risk factors, we built the multivariate models using conditional logistic regression techniques[13]. Besides the effects on all-stroke risk, we analysed the effects on haemorrhagic and ischaemic stroke, respectively, by restricting the analyses to the relevant matched case–control sets. A *P* value ≤0·05 was considered statistically significant.

British Journal of Nutrition

The statistical computations were carried out using SPSS for Windows (version 11.5; SPSS Inc., Chicago, IL, USA) and EGRET for Windows (version 2.0; CYTEL Software Corporation, Cambridge, MA, USA).

Results

For the whole population, median levels of Hg and EPA + DHA were 3·63 ng Hg/g erythrocytes and 5·75 %, respectively, while mean fish intake was 1·43 meals/week. Among cases, diabetes, hypertension and daily smoking were significantly more common. Cases had higher serum cholesterol and BMI than controls (Table 1).

In the first part of the series of consecutive cases and their referents, we analysed EPA + DHA in plasma phospholipids, while in the latter part in erythrocyte membranes. The levels in these two series did not differ substantially. Nevertheless, we evaluated the effect of modification of series; no such effect was present ($P=0·96$).

Fish intake was positively correlated with erythrocyte Hg content ($P<0·001$; Fig. 1) and EPA + DHA ($P<0·001$; Fig. 2). There was a strong correlation between Hg and EPA + DHA (Table 2).

In the univariate analyses, fish intake, but not erythrocyte Hg content or EPA + DHA, were associated with stroke risk (Table 3).

Table 1. Baseline characteristics for controls, all stroke patients and patients with ischaemic and haemorrhagic stroke (Mean values and standard deviations)

				Strokes					
		Controls (*n* 738)		All (*n* 369)		Ischaemic (*n* 302)		Haemorrhagic (*n* 60)	
	n	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)									
Men	666	54·6	8·2	54·6	8·2	54·9	8·0	54·1	8·6
Women	441	55·4	8·0	55·4	8·1	55·0	8·2	57·4	6·8
Smokers (%)									
Men	649	20·0		25·6		24·3		26·8	
Women	419	17·2		26·4*		26·0		33·3	
Self-reported diabetes (%)									
Men	650	2·06		7·48*		8·28		4·76	
Women	422	1·06		3·55		3·25		0	
Academic education (%)									
Men	632	14·7		13·3		13·3		12·5	
Women	411	15·3		14·6		15·8		6·25	
Hypertension (%)									
Men	654	25·2		44·0*		39·1		61·4	
Women	431	28·4		38·7*		37·1		50·0	
Diastolic BP (mmHg)									
Men	651	86	10	91*	11	89	11	95	10
Women	429	84	9	88*	9	87	9	91	10
Systolic BP (mmHg)									
Men	651	136	18	144*	19	142	19	153	17
Women	429	137	19	145*	23	144	23	148	20
Serum cholesterol (mmol/l)									
Men	651	6·07	1·19	6·34*	1·37	6·41	1·39	6·05	1·19
Women	433	6·37	1·30	6·53	1·34	6·51	1·35	6·33	1·07
BMI (kg/m^2)									
Men	646	26·1	3·2	26·9*	3·6	26·6	3·3	28·0	4·2
Women	434	26·0	4·3	27·3*	5·2	27·2	5·1	27·2	5·4
Fish intake (meals/week)									
Men	616	1·30	1·29	1·47	1·27	1·42	1·20	1·59	1·45
Women	415	1·56	1·45	1·55	1·42	1·52	1·37	1·32	0·73
Erythrocyte Hg (ng/g)†									
Men	599	3·72	3·71	3·68	3·03	3·86	3·09	3·68	2·88
Women	394	3·55	3·80	3·43	3·22	3·39	3·01	4·24	4·59
EPA (%)†									
Men	638	1·29	0·48	1·30	0·55	1·31	0·52	1·26	0·68
Women	430	1·29	0·53	1·30	0·51	1·32	0·51	1·15	0·50
DHA (%)†									
Men	634	4·35	1·00	4·44	0·98	4·47	1·01	4·32	0·82
Women	429	4·62	1·06	4·57	1·08	4·62	1·08	4·14	1·15
EPA + DHA (%)†									
Men	634	5·61	1·33	5·78	1·36	5·85	1·38	5·65	1·31
Women	429	5·88	1·43	5·81	1·45	5·91	1·45	5·15	1·52

BP, blood pressure; EPA + DHA, sum of proportions of EPA and DHA.
* Percentage or mean value was significantly different from that of the control group ($P\leq 0·05$).
† Values are medians.

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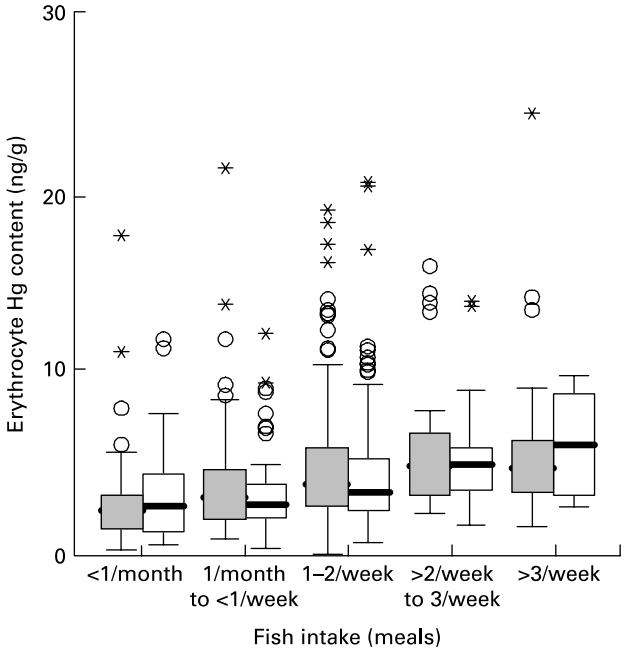

Fig. 1. Hg levels in erythrocyte membranes in categories with different fish intake (R_s 0·29 ($P \leq 0{\cdot}001$) for men; R_s 0·30 ($P \leq 0{\cdot}001$) for women). Each box shows the median and quartiles for men (▩) and women (□). Outliers (○) and extremes (*) are shown. Erythrocyte Hg values over 30 ng/g erythrocytes (*n* 3) are excluded.

For multivariate analysis, serum cholesterol level, smoking, BMI, diabetes and blood pressure were selected as candidate risk factors, besides fish intake. Serum cholesterol level did not contribute significantly to the multivariate model, and did not noticeably affect the effect estimates of the other candidate risk determinants. Therefore serum cholesterol was not included in the final multivariate model.

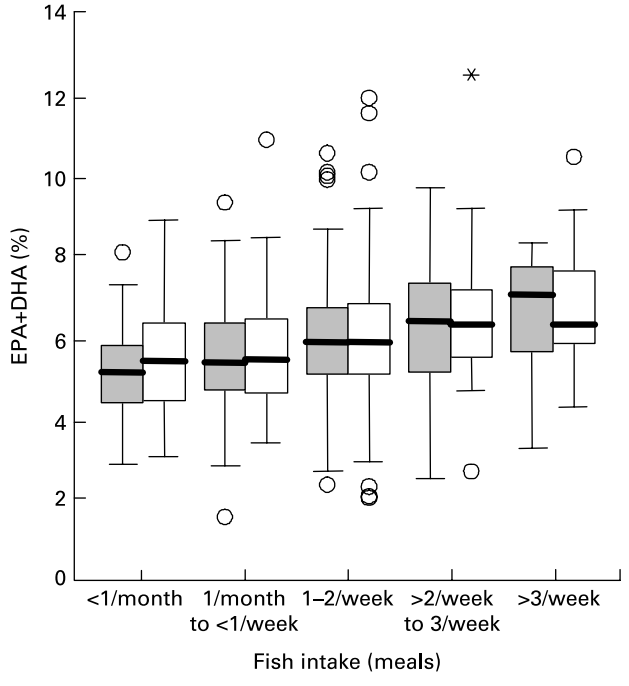

Fig. 2. Sum of proportions of EPA and DHA in plasma phospholipids (113 cases; 226 controls) and in erythrocyte membranes (256 cases; 512 controls) in categories with different fish intake (R_s 0·26 ($P \leq 0{\cdot}001$) for men; R_s 0·22 ($P \leq 0{\cdot}001$) for women). Each box shows the median and quartiles for men (▩) and women (□). Outliers (○) and extremes (*) are shown.

The effect of fish intake was significantly modified by sex ($P = 0{\cdot}03$). There was an association between increased risk for all types of stroke and high fish intake in males (Table 4, Fig. 3) and the association with stroke was only marginally different for reported intake of fatty fish, compared with lean fish (Table 4). Reported lean and fatty fish intakes were clearly correlated (Table 2). In females high fish intake was non-significantly associated with decreased risk for stroke (Table 4, Fig. 3). The OR shown in Fig. 3 are in accordance with the model assumption of a multiplicative risk used in Tables 2 and 3. The estimated effect of fish intake on stroke risk did not differ greatly when restricting the multivariate analysis to ischaemic (83 % of the cases) or haemorrhagic stroke (Table 4).

In order to investigate the influence of the biomarkers EPA + DHA and Hg on risk, we replaced fish intake in the multivariate model with these, one at a time. Then, for men, there was no statistically significant increase of the risk for all strokes, neither for EPA + DHA (OR 1·08 (95 % CI 0·92, 1·28)), nor for Hg (OR 0·99 (95 % CI 0·93, 1·06)). For ischaemic stroke in men, there was an almost statistically significant increase of the risk for EPA + DHA (OR 1·20 (95 % CI 0·99, 1·46)), but not for Hg (OR 1·00 (95 % CI 0·93, 1·07)). For women, there was no association between all-stroke risk and EPA + DHA (OR 0·98 (95 % CI 0·81, 1·17)) or Hg (OR 1·00 (95 % CI 0·94, 1·08)). A similar lack of statistically significant associations was obtained for ischaemic stroke in women (data not shown).

Since the variable hypertension also includes use of anti-hypertensive medication, this variable, instead of systolic or diastolic blood pressure, was selected for the multivariate analysis. When hypertension was replaced by systolic or diastolic blood pressure, only minor changes occurred. With systolic blood pressure instead of hypertension, the OR for fish intake changed from 1·24 (95 % CI 1·01, 1·51) to 1·26 (95 % CI 1·03, 1·54) for men. Exchange to diastolic blood pressure changed the OR to 1·27 (95 % CI 1·04, 1·55) for men. No changes were detected for women. Statistical analysis with systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, or reported use of anti-hypertensive medication during the last 14 d, as cut-offs for hypertension, gave results similar to those with the cut-off limits of 160/95; for men, the OR for fish intake changed from 1·23 to 1·28, still significant, and for women the OR for fish intake changed from 0·90 to 0·93, still non-significant. Effects of other risk factors also changed only marginally; the greatest change was found for hypertension, where the OR increased from 2·13 (95 % CI 1·54, 2·95) to 2·74 (95 % CI 1·94, 3·86).

Discussion

Fish intake was associated with an increased risk for stroke, but only in men. Neither Hg, nor EPA + DHA, was associated with the risk of total stroke, although a non-significant tendency was observed for ischaemic stroke and EPA + DHA in men. Since there were few haemorrhagic stroke cases in each group, when men and women were separated, no conclusive results can be drawn on risk of

British Journal of Nutrition

Table 2. Spearman rank correlations (bivariate analyses) between risk factors for stroke and factors associated with fish intake in 369 cases and 738 controls†

	Fish	Lean fish	Fatty fish	Erythrocyte Hg	EPA + DHA
Men					
Lean fish	0·78***	–			
Fatty fish	0·71***	0·22***	–		
Erythrocyte Hg	0·31***	0·20***	0·30***	–	
EPA + DHA	0·28***	0·14***	0·27***	0·44***	–
Serum cholesterol	0·020	0·002	0·030	0·056	−0·013
Smoking	−0·055	−0·043	−0·034	−0·038	−0·060
BMI	−0·001	−0·039	0·047	0·095*	0·12**
Diabetes	0·041	0·098*	−0·059	0·031	−0·021
Hypertension	0·025	−0·004	0·038	0·018	0·12**
SBP	0·014	−0·064	0·071	0·037	0·041
DBP	0·048	0·000	0·082*	0·015	0·069
Age	0·005	−0·031	0·053	0·12**	0·17***
Women					
Lean fish	0·77***	–			
Fatty fish	0·74***	0·26***	–		
Erythrocyte Hg	0·33***	0·16**	0·30***	–	
EPA + DHA	0·24***	0·16**	0·24***	0·50***	–
Serum cholesterol	0·063	0·030	0·12*	0·15**	0·068
Smoking	−0·095	−0·067	−0·089	−0·10*	−0·13**
BMI	0·18***	0·18***	0·13*	0·031	0·030
Diabetes	0·049	0·046	0·026	−0·017	−0·038
Hypertension	0·047	−0·040	0·10*	−0·027	0·052
SBP	0·12*	0·051	0·15**	−0·005	0·058
DBP	0·12*	0·023	0·15**	−0·029	0·001
Age	0·028	−0·11*	0·18***	0·086	0·079

EPA + DHA, sum of proportions of EPA and DHA; SBP, systolic blood pressure; DBP, diastolic blood pressure.
Correlation was significant: *$P \leq 0{\cdot}05$, **$P \leq 0{\cdot}01$, ***$P \leq 0{\cdot}001$.
† Men: cases (*n* 222) and controls (*n* 444); women: cases (*n* 147) and controls (*n* 294).

haemorrhagic stroke. However, for fish intake and risk of haemorrhagic stroke, the trend was similar to that of ischaemic stroke.

Despite nominal statistical significance of the relationship of fish intake with stroke in men, and of a different relationship of fish intake with stroke in women than in men, we cannot completely rule out that the present findings are due to chance. First, we made several comparisons and have made no adjustment for multiple comparisons. Second, relatively few participants were found outside the one to two meals/week category, so we have limited power to estimate risk at high and low fish intake. Nevertheless, the data

Table 3. Univariate conditional logistic regression analyses concerning the influence of potential risk factors on all-stroke risk, based on 369 matched sets of one case and two controls

Risk factor	Unit or category	Missing cases (*n*)	Missing controls (*n*)	OR*	*P*†
Fish-related risk factors					
Fish intake	Meals/week	30	46	1·13	0·05
Lean fish intake	Meals/week	24	36	1·12	0·19
Fatty fish intake	Meals/week	22	37	1·17	0·07
Hg in erythrocytes	ng/g	34	80	1·00	0·84
EPA+DHA	%	9	35	1·02	0·66
Background risk factors					
Serum cholesterol	mmol/l	8	15	1·16	0·004
Smoking	No	14	25	1·0	0·008
	Yes			1·54	
BMI	Kg/m^2	8	19	1·06	<0·001
Self-reported diabetes	No	14	21	1·0	<0·001
	Yes			3·70	
Academic education	No	21	43	1·0	0·56
	Yes			0·89	
Hypertension	No	9	13	1·0	<0·001
	Yes			2·17	
Diastolic BP	mmHg	12	15	1·05	<0·001
Systolic BP	mmHg	12	15	1·03	<0·001

EPA + DHA, sum of proportions of EPA and DHA; BP, blood pressure.
*OR, reflecting multiplicative increase in risk per unit increase for non-categorical risk factors, or in relation to the reference category (with OR 1·0) for categorical risk factors.
† From the Wald test, reflecting the degree of influence of the potential risk factor.

British Journal of Nutrition

Table 4. Multivariate conditional logistic regression analyses concerning the effects of the candidate risk factors on all-stroke risk, ischaemic stroke risk and haemorrhagic stroke risk†

Risk factor	Unit	Cases (*n*)	Controls (*n*)	OR‡	95 % CI	*P*
All-stroke risk						
Total fish intake*	Meals/week					
Males		189	342	1·24	1·01, 1·51	0·04
Females		128	228	0·90	0·73, 1·12	0·35
Fatty fish intake	Meals/week					
Males		195	356	1·29	0·95, 1·83	0·06
Females		129	231	0·82	0·58, 1·15	0·24
Lean fish intake	Meals/week					
Males		194	352	1·23	0·94, 1·62	0·14
Females		128	232	0·98	0·74, 1·30	0·91
Ischaemic stroke risk						
Total fish intake	Meals/week					
Males		147	271	1·25	1·00, 1·56	0·04
Females		111	197	0·93	0·74, 1·17	0·51
Fatty fish intake	Meals/week					
Males		152	282	1·25	0·93, 1·65	0·14
Females		112	200	0·91	0·64, 1·28	0·58
Lean fish intake	Meals/week					
Males		152	281	1·33	0·97, 1·82	0·07
Females		112	201	0·96	0·70, 1·30	0·77
Haemorrhagic stroke risk						
Total fish intake	Meals/week					
Males		39	65	1·14	0·69, 1·88	0·59
Females		15	27	0·61	0·23, 1·57	0·31
Fatty fish intake	Meals/week					
Males		40	68	1·42	0·71, 2·85	0·32
Females		15	27	0·28	0·07, 1·10	0·07
Lean fish intake	Meals/week					
Males		39	65	0·86	0·38, 1·93	0·71
Females		15	27	1·11	0·54, 2·29	0·77

* The effect of fish intake was significantly modified by sex ($P=0·03$).
† Diabetes, hypertension, BMI and smoking are included in the model, in addition to fish intake.
‡ OR, reflecting multiplicative increase in risk per unit increase for the (non-categorical) risk determinants of fish intake.

showed increased stroke risk in men in the more than two meals/week categories.

The results were not anticipated. A difference between men and women is not surprising (see later), but we had expected an association with Hg and/or EPA + DHA, since these agents have been implicated in prior studies. EPA + DHA was associated with a trend of an increased risk for ischaemic stroke in men; this was opposite to the expected, but may be explained by the fact that EPA and DHA are known biomarkers for fish intake[16]. There was a fairly close association between fish intake and concentrations of Hg and EPA + DHA, indicating that the estimation of fish intake from questionnaires is valid. Therefore, the question arises if the present results are only an effect of random variation or if they indicate that another causative agent than Hg is present in fish.

The lack of associations between stroke risk and Hg is not due to analytical errors; the analytical methods for Hg and EPA + DHA showed good precision. We only analysed total Hg concentrations. Since the dominating Hg species in erythrocyte membranes in this region of Sweden is methyl Hg, we assume that it is acceptable to analyse total Hg[17]. The exposure level of Hg was low in this population, which may explain the lack of association with stroke risk. We chose to include the sum of proportions of EPA and DHA, since separate analysis did not contribute further.

A strength of the present study design is that the blood samples were obtained before the event. However, they only reflect a relatively short time period, often years before the onset of the stroke, and the levels change fairly rapidly after an alteration in intake of methyl Hg[18] and EPA + DHA. However, this is not a problem, since it is well known that fish intake habits prevail for long time periods[19].

In statistical modelling, we analysed possible confounders. Adjustment for matching factors was inherent in the design. We also included other factors (smoking, BMI, cholesterol, diabetes, hypertension) associated with stroke, thus representing potential confounders. We used hypertension rather than diastolic and systolic blood pressure, since the latter are affected by medication. Only minor changes were detected when hypertension was replaced by diastolic or systolic blood pressure.

In the present study, increased levels of Hg and EPA + DHA were not associated with a decreased risk of stroke. This differs from the picture seen in the same region of Sweden for AMI, in which both Hg and EPA + DHA were predictors of a decreased risk[16], most likely because they are indicators of fish intake, a possible preventive factor for AMI[20,21]. In the present study fish intake seemed to be associated with increased risk of ischaemic stroke in men, but the effect appears to be small compared with the protective effect on AMI.

British Journal of Nutrition

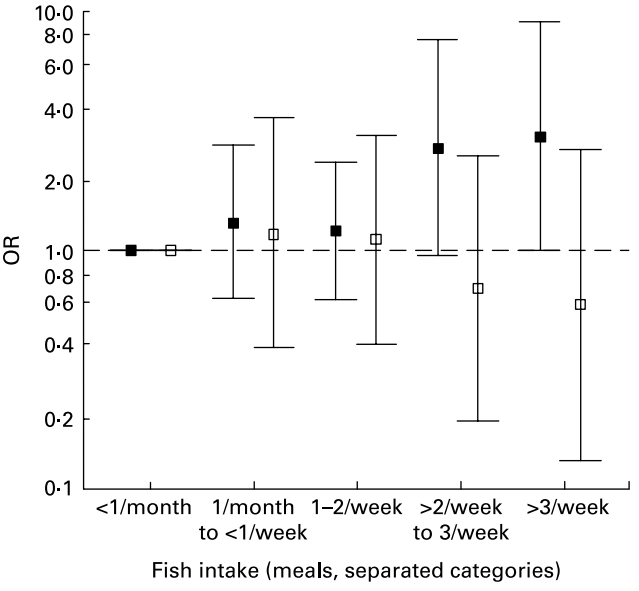

Fig. 3. Effects of fish intake on all-stroke risk in men (■) and women (□), by five categories of fish intake in a multivariate model including also smoking, diabetes, hypertension and BMI. The numbers of cases and controls in each category that contributed to the multivariate model were: 15 + 45 (<1 meal/-month), 39 + 72 (≥1 meal/month to <1 meal/week), 106 + 234 (1–2 meals/week), 17 + 25 (>2 to ≤3 meals/week) and 12 + 15 (>3 meals/week) for males; 7 + 19, 22 + 45, 81 + 147, 10 + 28 and 8 + 19 for females. Values are OR, with 95% CI represented by vertical bars, for different categories of fish intake, which is different from Tables 3 and 4 where OR is calculated per meal per week.

The present lack of a protective effect of EPA + DHA on stroke is in accordance with some other investigations[22,23] and with the general concept that stroke is associated with other risk factors than AMI.

The present data indicate that fish intake is a risk determinant. This is contrary to the meta-analyses by He *et al.*[1] and Bouzan *et al.*[2], but in accordance with some previous data[23,24]. The increased stroke risk appears at relatively high fish intake (more than two meals/week) and only in men. A sex difference similar to the one that appeared in the present study has been observed in previous studies of stroke[4] and IHD[25]. Therefore, explanations of the conflicting results from different studies may lie in (a) the unknown shape of the dose–response curve, which may have a threshold or be U- or J-shaped, and (b) different effects in men and women. It is also possible that the associations of fish consumption with other lifestyle habits, which may appear as predictors of stroke, differ between populations.

Further clarification of the epidemiology of stroke and fish intake is hampered by the fact that the mechanism behind the effect of fish is not known. In the present study, it is most probably not due to Hg. Thus, other contaminants in fish should be considered. One of the most prevalent in fish in Sweden, and other areas, is persistent organic halogenated pollutants[26,27], but we know of no evidence that those cause vascular disease. Fish intake gives exposure to amines[28], which may react with nitrite in the stomach to form nitrosamines, known mutagens, which hypothetically may induce atherosclerosis.

Conclusion

The effect of fish intake on stroke risk seems to be different in men and women. There was no decrease in stroke risk with increased levels of EPA + DHA, and no association between stroke risk and Hg could be demonstrated at these low levels. Even if fish intake may be a risk determinant for ischaemic stroke in men, this does not mean that we recommend a reduction of fish consumption. If there is a factor in fish increasing stroke risk in men, it should be identified, and – if possible – eliminated.

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