n−3 Fatty acids consumed from fish and risk of atrial fibrillation or flutter: the Danish Diet, Cancer, and Health Study[1–3]

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ABSTRACT

Background: Experimental studies have shown that n−3 polyunsaturated fatty acids in fish may have antiarrhythmic properties.

Objective: We examined the association between consumption of n−3 fatty acids from fish and risk of atrial fibrillation or flutter.

Design: In a prospective cohort study of 47 949 participants (mean age: 56 y) in the Danish Diet, Cancer, and Health Study, we investigated the relation between the consumption of n−3 fatty acids from fish estimated from a detailed semiquantitative food questionnaire and risk of atrial fibrillation or flutter. The subjects were followed up in the Danish National Registry of Patients for the occurrence of atrial fibrillation or flutter and in the Danish Civil Registration System (vital status and emigration). The consumption of n−3 fatty acids from fish was analyzed as sex-specific quintiles with the use of Cox proportional hazards models.

Results: During follow-up ($\bar{x}$: 5.7 y), atrial fibrillation or flutter had developed in 556 subjects (374 men and 182 women). When the lowest quintile of n−3 fatty acids consumed from fish was used as a reference, the unadjusted hazard rate ratios in quintiles 2, 3, 4, and 5 were 0.93, 1.11, 1.10, and 1.44, respectively (*P* for trend = 0.001). The corresponding adjusted hazard rate ratios were 0.86, 1.08, 1.01, and 1.34 (*P* for trend = 0.006). Inclusion of information on the frequency of fatty fish consumption did not alter these associations.

Conclusions: Consumption of n−3 fatty acids from fish was not associated with a reduction in risk of atrial fibrillation or flutter. We cannot exclude the possibility of residual confounding caused by a lack of information on intake of fish-oil tablets. *Am J Clin Nutr* 2005;81:50–4.

KEY WORDS Arrhythmia, cohort studies, diet, epidemiology, fish oils, nutrition, Danish Diet, Cancer, and Health Study

INTRODUCTION

Experimental studies have suggested that n−3 polyunsaturated fatty acids, mainly from fish or fish-oil capsules, may have antiarrhythmic properties (1–5). Recently, it was confirmed that n−3 fatty acids block the cardiac Na^+ channels in rat ventricular myocytes (6), and a small nonblinded, nonrandomized pilot study in 10 patients with an implanted cardioverter defibrillator showed a reduction in the inducibility of sustained ventricular tachycardia after infusion of n−3 fatty acids (7). We therefore examined the association between consumption of n−3 polyunsaturated fatty acids from fish and the risk of atrial fibrillation or flutter in the Danish Diet, Cancer, and Health Study.

SUBJECTS AND METHODS

Study population

The Danish Diet, Cancer, and Health Study is a prospective cohort study with the primary aim of studying the role of diet in cancer risk but with a potential for studying other diseases as well. The study design was described in detail elsewhere (8, 9).

From December 1993 through May 1997, 80 996 men and 79 729 women aged 50 to 64 y were invited to participate in the study; 27 177 men and 29 876 women accepted the invitation. Eligible cohort members were born in Denmark, living in the Copenhagen and Aarhus areas, and had no previous cancer diagnosis in the Danish Cancer Registry. The baseline data were linked to the Danish Cancer Registry and other population-based registries, including the Danish National Registry of Patients, and the Danish Civil Registration System, using the civil registry number, which is a unique number given to everyone with an address living in Denmark since 1968. The Civil Registration System has electronic records of all changes in vital status for the Danish population since 1968, including change in address, date of emigration, and date of death. The Danish National Registry of Patients was established in 1977, and has records for 99.4% of all discharges from nonpsychiatric hospitals in Denmark (10). The data include the civil registry number, dates of admission and discharge, surgical procedures performed, and up to 20 discharge diagnoses per discharge, classified until 1993 according to the Danish version of the International Classification of Diseases, 8th revision, and thereafter according to the national version of International Classification of Diseases, 10th revision. The physician who discharged the patient coded all discharge diagnoses. To study incident cases of atrial fibrillation, and to reduce confounding, we excluded participants who had been hospitalized before baseline with endocrine diseases or cardiovascular diseases others than hypertension, recorded in the National Registry of Patients, International Classification of Diseases, 8th revision codes: 240–279, 390–398, and 410–458, and International

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Classification of Diseases, 10th revision codes: E00-E90, I00-I09, I16-I99. We did not exclude patients with hypertension before or at baseline for several reasons. First, the diagnostic criteria for hypertension have changed over the last decades. Second, the validity of a diagnosis of hypertension in the Danish National Registry of Patients is low (11). Third, if we used a definition of hypertension as a systolic blood pressure > 140 mm Hg at baseline, we would exclude >50% of subjects from the cohort (8). Finally, we did not a priori feel that the relation between blood pressure and risk of atrial fibrillation included a threshold function, which allowed us to exclude any subject from the cohort who had a specific level of blood pressure. The Danish Diet, Cancer, and Health Study and the present study were approved by the Regional Ethics Committees in Copenhagen and Aarhus and by The Danish Data Protection Agency.

Baseline data

Height, weight, systolic and diastolic blood pressure, and total serum cholesterol were measured at baseline. Body weight was measured with the use of a digital scale weight (Soehnle, Germany) and was recorded to the nearest 100 g. Blood pressure (systolic and diastolic) were measured with an automatic blood pressure measurement devise (Takeda UH 751, Tokyo). Nonfasting total serum cholesterol was measured according to national guidelines (12).

All participants filled in a questionnaire about medical diseases, including myocardial infarction, angina, stroke, hypertension, hypercholesterolemia, and diabetes, and drug treatment for those conditions. Subjects who reported to have ischemic heart disease, stroke, or diabetes or who were medicated for those conditions were excluded from the present study. The participants also completed a questionnaire about smoking habits, alcohol intake, health, and duration of education.

Dietary intake of n−3 fatty acids from fish

All cohort members completed a detailed semiquantitative food- and drink-frequency questionnaire. The study participants were asked to fill in a questionnaire about type and frequency of fish consumption (never, less than once per month, once per month, 2–3 times/mo, once per week, 2–4 times/wk, 5–6 times/wk, once per day, 2–3 times/d, 4–5 times/d, 6–7 times/d, and ≥8 times/d). The daily intake of specific foods and nutrients was computed from the food-frequency questionnaire for each participant with the use of the software program FOODCALC (13). Standard recipes and sex-specific portion sizes were applied to calculate intake in grams per day with the use of data from different sources, ie, the 1995 Danish National Dietary Survey (14), 24-h diet-recall interviews from 3818 of the study participants (15), and various cookery books.

Descriptions of the development and validation of the food-frequency questionnaire were published previously (16, 17). A biomarker study was carried out to validate the information on dietary intake of fatty acids, including marine n−3 polyunsaturated fatty acids. This study showed correlation coefficients (Pearson) between the reported dietary intake in the food-frequency questionnaire and the relative fat tissue composition of the marine fatty acids eicosapentaenoic acid and docosahexaenoic acid of 0.47 and 0.41, respectively (18). The exposure evaluated in the present study was the consumption of n−3 fatty acids from fish estimated from the food-frequency questionnaire.

We categorized the following species of fish (which are available and eaten in Denmark) as fatty fish: herring, mackerel, sardine, trout, and salmon. We converted the exposure information into 2 variables: *1*) the amount (g) of marine n−3 polyunsaturated fatty acids consumed (per day) from any species of fish and evaluated as sex-specific quintiles and *2*) the frequency of consumption of fatty fish (<2 or ≥2 times/wk).

Identification of incident atrial fibrillation and atrial flutter

The general health and hospital care systems in Denmark are no-charge and nonprofit systems that are financed through taxes. During the study period there was a very limited capacity in private specialist practices and in private hospitals. We identified probable cases of atrial fibrillation or flutter within the cohort in The Danish National Registry of Patients, ie, cases with the discharge diagnoses 427.93, 427.94, and I48 through 31 December 31 2001. Beginning from 1 January 1995, patients who were only seen in an outpatient hospital clinic were also coded into the Danish National Registry of Patients. A change from the International Classification of Diseases 8th revision to the International Classification of Diseases 10th revision occurred in Denmark in 1994. Atrial fibrillation and atrial flutter were coded separately in the International Classification of Diseases 8th revision (codes 427.93 and 427.94); however, in the International Classification of Diseases 10th revision, atrial fibrillation and flutter have the same code (I48).

A single reviewer (LF), using a standardized form, reviewed the medical records of the subset of study participants living in the county of Aarhus with an incident diagnosis of atrial fibrillation or flutter recorded in the Danish National Registry of Patients through December 1999. Of 116 subjects with an incident diagnosis of atrial fibrillation or flutter, an electrocardiogram, a printout from telemetry, or a printout from a Holter recording verified atrial fibrillation or atrial flutter in 112 subjects. Thus, diagnoses for 112 of the 116 subjects (97%) were verified. Of the 112 subjects with a verified diagnosis, 103 subjects (92%) had atrial fibrillation, 3 (3%) had both atrial fibrillation and atrial flutter, and 6 (5%) had atrial flutter.

Follow-up

The study participants were followed-up in the National Registry of Patients and in the Central Person Registry. Linking was done by using the civil registry number. Follow-up for atrial fibrillation or flutter began on the date of visit to one of the study centers and ended on the date of an event or a censoring (ie, a diagnosis of atrial fibrillation or flutter, death, emigration, or 31 December 2001, whichever came first).

Statistical methods

We used piecewise linear regression to examine the relation between a continuous variable and the hazard of atrial fibrillation or flutter (19). We kept a continuous variable as continuous in the Cox regression model, when appropriate, according to these analyses.

We computed a multivariate Cox regression model by an initial forced entry of known risk factors for atrial fibrillation, namely age, sex, body height, body mass index, alcohol consumption, systolic blood pressure, and treatment for hypertension, followed by forward selection of other variables of interest.

TABLE 1
Baseline characteristics of the subjects in the Danish Diet, Cancer, and Health Study according to sex-specific quintiles of n−3 polyunsaturated fatty acid (PUFA) intake from fish

Characteristic	Quintile 1 (n = 9589)	Quintile 2 (n = 9590)	Quintile 3 (n = 9591)	Quintile 4 (n = 9590)	Quintile 5 (n = 9589)	*P* for correlation[1]
n−3 PUFA intake from fish (g/d)	0.16 ± 0.08[2]	0.36 ± 0.06	0.52 ± 0.07	0.74 ± 0.10	1.29 ± 0.47	—
Intake of fatty fish ≥ 2 times/wk (%)	0.4	12.2	50.4	84.1	96.6	< 0.01
Total energy intake (kJ/d)	8748 ± 2531	9127 ± 2438	9559 ± 2496	10053 ± 2576	11140 ± 3045	< 0.01
Age (y)	55.5 ± 4	55.7 ± 4	55.9 ± 4	56.2 ± 4	56.9 ± 4	< 0.01
Sex, men (%)	47.0	47.0	47.0	47.0	47.0	
Body height (cm)	169.9 ± 9	170.2 ± 9	170.2 ± 9	170.2 ± 9	170.0 ± 9	0.35
BMI (kg/m^2)	25.9 ± 4.0	25.9 ± 4.0	25.9 ± 3.9	25.9 ± 3.9	25.9 ± 4.0	0.08
Smoking[3]						
Never (%)	37	36	38	36	35	—
Former (%)	27	28	29	29	28	—
Current (%)	36	35	34	35	37	0.12
Alcohol intake (g/d)	18.4 ± 22	20.2 ± 21	21.0 ± 21	21.6 ± 21	21.8 ± 22	< 0.01
Systolic blood pressure (mm Hg)	138 ± 20	139 ± 20	139 ± 20	139 ± 20	140 ± 20	< 0.01
Treatment for hypertension (%)	9.9	9.8	10.0	10.4	11.4	< 0.01
Total cholesterol > 6 mmol/L (%)	48.1	49.0	48.7	50.4	52.4	< 0.01

[1] Spearman correlation analysis. Not all significant digits are shown in the table (ie, values have been rounded). Because of the large number of subjects, some of the significant differences were due to decimal places not shown.
[2] $\bar{x}$ ± SD (all such values).
[3] Sum of percentages may not add up to 100 because of rounding.

We performed supplementary analyses by adding product terms to test for interaction. The relevance of a variable in the model was further assessed by the change-in-estimate method (20). The variables included in our final model were age (y), sex, body height (cm), body mass index (kg/m^2), systolic blood pressure (mm Hg), treatment for hypertension (yes or no), total serum cholesterol > 6 mmol/L (yes or no), alcohol consumption (g/d), and sex-specific quintile of fish-oil consumption. Thereafter, we assessed further potential confounders: total daily energy intake (kJ/d), frequency of consumption of fatty fish, smoking (never, former, or current), and length of education after elementary school (0, <3, 3–4, or >4 y) to evaluate the potentials for a change in the estimate of the hazards for atrial fibrillation or flutter associated with consumption of fish oil.

Correlation was evaluated by Spearman's nonparametric correlation analysis. Tests for linear trend were calculated by assigning the medians of intake in quintiles treated as a continuous variable. The assumption of proportional hazards in the Cox models was evaluated with the use of graphic assessment and was found to be appropriate in all models. We calculated 95% CIs throughout the analyses. We used SPSS statistical software version 11.5 (SPSS Inc, Chicago).

RESULTS

The cohort included 57 053 subjects at baseline. We excluded 9022 subjects who reported to have taken or who were taking medicine for endocrine or cardiovascular diseases (hypertension was not excluded), to have a diagnosis of endocrine or cardiovascular disease (hypertension was not excluded) in the Danish National Registry of Patients before or at baseline, or who met both criteria. Eighty-two subjects were excluded because of missing information on fish-oil consumption. Thus, the study population included in the cohort consisted of 47 949 subjects, 22 528 men and 25 421 women. The men provided a total of 128 131 person-years of risk ($\bar{x}$: 5.7 y; range: 0–8.1 y), and the women contributed 147 251 person-years of risk ($\bar{x}$: 5.7 y; range: 0–8.1 y). During follow-up, 374 men (1.7%) and 182 women (0.7%) had an incident diagnosis of atrial fibrillation or flutter in the National Registry of Patients, which corresponded with incidence rates of 29.1/10 000 person-years at risk in men and 12.4/10 000 person-years at risk in women.

Characteristics at baseline according to sex-specific quintiles of consumption of n−3 fatty acids from fish are shown in **Table 1**. The mean consumption of fish oil was 0.16 g/d in the lowest quintile compared with 1.29 g/d in the top quintile. Mean age, consumption of alcohol, systolic blood pressure, and the proportion of subjects receiving treatment for hypertension increased by increasing category of fish-oil consumption.

The incidence rates by increasing sex-specific quintiles of fish-oil consumption were 18.1, 16.7, 20.0, 20.0, and 26.2 per 10 000 person-years of follow-up (**Table 2**). The risk of atrial fibrillation or flutter according to sex-specific quintiles of intake of marine n−3 polyunsaturated fatty acids is shown in Table 2. When the lowest sex-specific quintile of fish-oil consumption was used as a reference, the adjusted hazard rate ratios in quintiles 2, 3, 4, and 5 were 0.86, 1.08, 1.01, and 1.34 (*P* value for trend 0.006). Information on the frequency of consumption of fatty fish (≥2 times/wk or <2 times/wk) did not change these estimates.

The risk of atrial fibrillation or flutter associated with exposure to n−3 fish oil from consumed fish did not change substantially by exposure to specific types of fish (mackerel, salmon, or herring) or by specific method of food preparation (data not shown). We did not observe any effect modification by sex or any other confounding variables.

DISCUSSION

In this large cohort study, we found that consumption of n−3 fatty acids from fish did not reduce the risk of atrial fibrillation or flutter. The lack of effect of fish oil in our study could have been

TABLE 2
Risk of atrial fibrillation or flutter according to sex-specific quintiles of n−3 polyunsaturated fatty acid (PUFA) intake from fish

	Quintile 1[1] (*n* = 9589)	Quintile 2 (*n* = 9590)	Quintile 3 (*n* = 9591)	Quintile 4 (*n* = 9590)	Quintile 5 (*n* = 9589)	*P* for trend[2]
n−3 PUFA intake from fish (g/d)	0.16 ± 0.08[3]	0.36 ± 0.06	0.52 ± 0.07	0.74 ± 0.10	1.29 ± 0.47	—
Mean duration of follow-up (y)	5.8	5.7	5.7	5.7	5.7	—
Person-years of follow-up (y)	55 193	55 013	54 766	55 111	55 051	—
Subjects with atrial fibrillation or flutter (*n*)	100	92	110	110	144	—
Incidence rate per 10 000 person-years	18.1	16.7	20.0	20.0	26.2	—
Unadjusted hazard rate ratio (95% CI)	1.00	0.93 (0.70, 1.23)	1.11 (0.85, 1.46)	1.10 (0.84, 1.45)	1.44 (1.12, 1.86)	0.001
Adjusted hazard rate ratio (95% CI)[4]	1.00	0.86 (0.65, 1.15)	1.08 (0.82, 1.42)	1.01 (0.77, 1.34)	1.34 (1.02, 1.76)	0.006

[1] Reference category.
[2] Tests for linear trend were calculated by assigning the medians of intake in quintiles treated as a continuous variable in a Cox proportional hazard model.
[3] $\bar{x}$ ± SD (all such values).
[4] Adjusted for age, sex, height, BMI, smoking, consumption of alcohol, total energy intake, systolic blood pressure, treatment for hypertension, total serum cholesterol, and level of education.

because the consumption of fish oil was insufficient to prevent arrhythmias. However, the mean consumption of marine n−3 polyunsaturated fatty acids in the top quintile was >1 g/d in men as well as in women, which was comparable with the daily supplement of 1 g n−3 polyunsaturated fatty acids used in the GISSI-Prevenzione Trial (2). Because we excluded subjects with known heart disease from our cohort, we cannot exclude the possibilities that fish oil may prevent the development of atrial fibrillation in patients with symptomatic heart disease or that fish oil may prevent relapses of atrial fibrillation in patients with paroxysmal atrial fibrillation.

The main strengths of our study were the large number of cases with atrial fibrillation; the detailed information on potential confounding factors, the complete follow-up through nationwide; population-based registries, which limit selection and surveillance bias; the standardized assessment of a sample of the registered outcome events; and a uniformly organized no-charge and nonprofit health care system. We used restriction in applying admissibility criteria to reduce confounding and to increase validity (21).

We had limited statistical power, and we were only able to include atrial fibrillation or flutter that was symptomatic and led to hospitalization or clinical investigation in an outpatient hospital clinic. However, given the age profile of our study cohort, it is likely that patients with symptoms of atrial fibrillation were referred to a hospital for further evaluation, and, during the study period, there was a limited capacity in private clinics and hospitals. We relied on self-reported data on consumption of fish, and we had no information on supplementary intake of fish oil from fish-oil capsules. However, a recent study on characteristics associated with the use of dietary supplements concluded that taking fish-oil supplements was associated with eating oil-rich fish (22). Thus, the problem in the present study does not seem to be misclassification of low exposure as high exposure and vice versa, because those already exposed to n−3 fish oil from eating fish may have added an additional exposure by taking fish-oil tablets. We recognize that some subjects categorized in the lowest quintiles of fish-oil intake may have taken fish-oil tablets, and this causes misclassification of exposure, which introduces bias toward unity. However, the major question raised in our study was as follows: do n−3 fatty acids from fish protect against atrial fibrillation? If fish oil has a protective role, we would have expected it to be seen in the top quintile of exposure, especially because we know that the consumption of fish-oil tablets is highest among those who eat much fatty fish.

Because of the multiple (>2) levels of exposure, bias introduced by misclassification of exposure may be toward as well as away from the null, depending on the categories to which the individuals are misclassified (21). Biased follow-up may have occurred if the unexposed subjects were underdiagnosed for atrial fibrillation or flutter more than were the exposed subjects (21). In the unadjusted analyses we found that increasing consumption of fish oil was associated with increased risk of atrial fibrillation or flutter. We also found that increasing intake of fish oil was associated with a slightly older age and with more subjects receiving treatment for hypertension. Older age and hypertension are not only risk factors for atrial fibrillation but are also risk factors for hospitalization, which often leads to the recording of an electrocardiogram, which will increase the probability of the detection of asymptomatic atrial fibrillation or flutter.

Substantial geographic variation exists in total fish intake and in intake of fatty fish between different countries. Of the 10 European countries participating in the European Investigations into Cancer and Nutrition (EPIC) Study, the greatest intake of very fatty fish was in the coastal areas of northern Europe (Denmark, Sweden, and Norway) (23). The intake of fish oil in Denmark is also higher than the mean intake of fish oil in the United States (4). We do not know whether fish oil has a protective effect against the occurrence of atrial fibrillation in populations with a low intake of fatty fish.

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LF designed the study, analyzed the data, and prepared the manuscript. PV reviewed the data analyses and the manuscript. LF received funding or grant support for research projects from Boeringer-Ingelheim, Cardiome Pharma, The Danish Heart Foundation, The Danish Medical Research Council, The Danish Society of Nephrology, The Hørslev Foundation, Laerdahls Foundation for Acute Medicine, Lægekredsforeningens Forskningsfond, Merk Sharp & Dome, Nycomed, and Pfizer and he serves or has served as a consultant for AstraZeneca and Pfizer. PV had no conflict of interest.

REFERENCES

1. Weylandt KH, Kang JX, Leaf A. Polyunsaturated fatty acids exert antiarrhythmic actions as free acids rather than in phospholipids. Lipids 1996;31:977–82.
2. Dietary supplementation with n−3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Lancet 1999;354:447–55.
3. Marchioli R, Barzi F, Bomba E et al. Early protection against sudden death by n−3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. Circulation 2002;105:1897–903.
4. Kris-Etherton PM, Harris WS, Appel LJ. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. Circulation 2002;106: 2747–57.
5. De Caterina R, Madonna R, Zucchi R, La Rovere MT. Antiarrhythmic effects of omega-3 fatty acids: from epidemiology to bedside. Am Heart J 2003;146:420–30.
6. Xiao YF, Ke Q, Wang SY, et al. Electrophysiologic properties of lidocaine, cocaine, and n−3 fatty-acids block cardiac Na^+ channels. Eur J Pharmacol 2004;485:31–41.
7. Schrepf R, Limmert T, Claus WP, Theisen K, Sellmayer A. Immediate effects of n−3 fatty acid infusion on the induction of sustained ventricular tachycardia. Lancet 2004;363:1441–2.
8. Tjonneland AM, Overvad OK. Diet, cancer and health—a population study and establishment of a biological bank in Denmark. Ugeskr Laeger 2000;162:350–4.
9. Riboli E, Hunt KJ, Slimani N, et al. European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. Public Health Nutr 2002;5:1113–24.
10. Andersen TF, Madsen M, Jorgensen J, Mellemkjoer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. Dan Med Bull 1999;46:263–8.
11. Nielsen HW, Tuchsen F, Jensen MV. Validity of the diagnosis "essential hypertension" in the National Patient Registry. Ugeskr Laeger 1996; 158:163–7.
12. Dyerberg J, Stender S, Andersen GE et al. Recommendations for clinical-chemical departments: lipid-lipoprotein analysis. Ugeskr Laeger 1990;152:1434–7.
13. Lauritsen J. FoodCalc 1.3. 1998. Internet: http://www.foodcalc (accessed 22 May 2004).
14. Warming DL. Danskernes kostvaner, teknisk rapport 2. (Eating habits in Denmark, technical report 2.) Copenhagen: The Danish Veterinary and Food Administration, 1997.
15. Slimani N, Deharveng G, Charrondiere RU, et al. Structure of the standardized computerized 24-h diet recall interview used as reference method in the 22 centers participating in the EPIC project. European Prospective Investigation into Cancer and Nutrition. Comput Methods Programs Biomed 1999;58:251–66.
16. Tjonneland A, Overvad K, Haraldsdottir J, Bang S, Ewertz M, Jensen OM. Validation of a semiquantitative food frequency questionnaire developed in Denmark. Int J Epidemiol 1991;20:906–12.
17. Overvad K, Tjonneland A, Haraldsdottir J, Ewertz M, Jensen OM. Development of a semiquantitative food frequency questionnaire to assess food, energy and nutrient intake in Denmark. Int J Epidemiol 1991;20: 900–5.
18. Tjonneland A, Overvad K, Thorling E, Ewertz M. Adipose tissue fatty acids as biomarkers of dietary exposure in Danish men and women. Am J Clin Nutr 1993;57:629–33.
19. Thomsen BL. A note on the modelling of continuous covariates in Cox's regression model. Copenhagen: University of Copenhagen, Statistical Research Unit, 1988. (Research Report 88/5.)
20. Greenland S. Modeling and variable selection in epidemiologic analysis. Am J Public Health 1989;79:340–9.
21. Rothman KJ. Epidemiology: an introduction. New York: Oxford University Press, 2002.
22. Harrison RA, Holt D, Pattison DJ, Elton PJ. Are those in need taking dietary supplements? A survey of 21 923 adults. Br J Nutr 2004;91:617–23.
23. Welch AA, Lund E, Amiano P, et al. Variability of fish consumption within the 10 European countries participating in the European Investigation into Cancer and Nutrition (EPIC) study. Public Health Nutr 2002; 5:1273–85.