

Fish, n-3 Fatty Acids, and Cardiovascular Diseases in Women of Reproductive Age

A Prospective Study in a Large National Cohort

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Abstract—Previous studies have indicated a protective effect of long-chain n-3 polyunsaturated fatty acids (LCn3FAs) against cardiovascular disease; however, women are underrepresented in cardiovascular research. The aim of this study was to explore the association between intake of LCn3FAs and the risk of cardiovascular disease in a large prospective cohort of young women (mean age at baseline: 29.9 years [range: 15.7–46.9]). Exposure information on 48 627 women from the Danish National Birth Cohort was linked to the Danish National Patients Registry for information on events of hypertensive, cerebrovascular, and ischemic heart disease used to define a combined measure of cardiovascular diseases. Intake of fish and LCn3FAs was assessed by a food-frequency questionnaire and telephone interviews. During follow-up (1996–2008; median: 8 years), 577 events of cardiovascular disease were identified. Low LCn3FA intake was associated with an increased risk of cardiovascular disease (adjusted hazard ratio for women in lowest versus highest LCn3FA intake group: 1.91 [95% CI: 1.26–2.90]). Restricting the sample to women who had consistently reported similar frequencies of fish intake across 3 different dietary assessment occasions tended to strengthen the relationship (hazard ratio for lowest versus highest intake: 2.91 [95% CI: 1.45–5.85]). Furthermore, the observed associations were consistent in supplementary analyses where LCn3FA intake was averaged across the 3 dietary assessment occasions, and the associations were persistent for all 3 of the individual outcomes. Our findings based on a large prospective cohort of relatively young and initially healthy women indicated that little or no intake of fish and LCn3FAs was associated with an increased risk of cardiovascular disease. (*Hypertension*. 2012;59:36-43.)

Key Words: cardiovascular diseases ■ fatty acids ■ epidemiology ■ follow-up study ■ women

Evidence from observational prospective studies,^{1–5} as well as randomized, controlled trials,^{6–8} suggests a protective effect of fish consumption and intake of the essential long-chain n-3 polyunsaturated fatty acids (LCn3FAs) against cardiovascular disease. The hypothesis of a beneficial cardiovascular effect of LCn3FAs originally stems from studies in the Greenland Inuit, where the incidence of coronary heart disease, and, in particular, acute myocardial infarction, was very low.⁹ Although findings have not been consistent,^{10,11} both previous and recent reviews have concluded that there is solid evidence of a protective effect of LCn3FAs against cardiovascular diseases,^{12–16} whereas, on the other hand, a much debated Cochrane review from 2004 concluded that it is unclear whether dietary or supplemental LCn3FAs alter the risk of cardiovascular events in high-risk groups or in the general population.¹⁷ A recent review of the cardiovascular effects of LCn3FAs concluded that, whereas there is evidence of several

beneficial cardiovascular effects of LCn3FAs, there are still many uncertainties in the field, for example, regarding arrhythmic events.¹⁸

Recently it has been emphasized by experts that cardiovascular risk in women is underestimated, and women are underrepresented in cardiovascular research.^{19,20} Even if most risk factors are shared by men and women, there might be sex differences with regard to their impact,²¹ and inflammation, high-density lipoprotein, and triglyceride levels might have a more negative influence on cardiovascular risk in women than in men.²¹ Because these risk factors are supposedly affected by LCn3FA intake, this underlines a need for studies on the importance of LCn3FAs in women.

The large birth cohorts that have emerged in several countries in the last decade provide information collected on a wide range of exposures and characteristics, which can facilitate such observational studies on etiologic associations in female populations. The aim of this study was to examine

Received July 7, 2011; first decision August 2, 2011; revision accepted October 12, 2011.

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Hypertension is available at <http://hyper.ahajournals.org>

DOI: 10.1161/HYPERTENSIONAHA.111.179382

the relationship between intake of fish and LCN3FAs and the risk of cardiovascular disease $\approx$ 8 years later in a large national pregnancy cohort.

Methods

Data for these analyses were derived from the Danish National Birth Cohort (DNBC), which is a nationwide study with >90 000 women enlisted. Eligible for recruitment were all pregnant women living in Denmark who were fluent in Danish. Enrollment took place at the first antenatal visit to the general practitioner, which is scheduled in gestation week 6 to 10, and an estimated 35% of all pregnancies in Denmark in the recruitment period from 1996 to 2002 were enrolled in the cohort.²² Mean age at baseline was 29.9 years (range: 15.7–46.9 years). Data collection instruments included 2 computer-assisted telephone interviews in gestation weeks 12 and 30 and a semiquantitative food frequency questionnaire (FFQ) that was mailed to the women in gestation week 25 and covered the diet during the previous month.²³

All of the participants provided written informed consent. The Regional Scientific Ethics Committee for the municipalities of Copenhagen and Frederiksberg approved all of the study protocols, and all of the procedures were in accordance with the Declaration of Helsinki.

Exposure

The fish species most frequently consumed by women in the DNBC were cod, plaice, salmon, herring, and mackerel, whereas species with high mercury content, such as shark and king mackerel, are not commonly consumed in Denmark.²⁴ Furthermore, during DNBC recruitment and initial data collection, dietary recommendations in Denmark did not include warnings regarding intake of fatty fish because of the potential harm of dioxins or methyl-mercury.

It can, still, be argued that diet measured during pregnancy might not reflect the women's habitual diet; however, dietary patterns have been shown to be relatively persistent from preconception through pregnancy and postpartum.²⁵ Furthermore, in a telephone interview 6 months postpartum, >90% of the women in the DNBC said that they had not changed their fish consumption during pregnancy (unpublished data).

Information on fish consumption was taken from the 2 telephone interviews and the FFQ. In the telephone interviews, participants were asked how often they consumed fish in a warm meal, a sandwich, or in a salad. The FFQ used in the DNBC contained >360 different food items and was a modified version of a questionnaire designed by the Danish Cancer Registry.²⁶ It has been validated in a subset of DNBC women against 7-day weighed food diaries and blood biomarkers²⁷ and includes detailed questions on frequency and type of fish consumed. Intake of LCN3FAs estimated from the FFQ correlated significantly with LCN3FAs quantified in erythrocyte lipids (Pearson correlation coefficient: 0.46 [95% CI: 0.36–0.55]; unpublished data). We defined 3 measures of exposure a priori, as described below.

Fish Intake Based on the FFQ

Total fish intake in grams per day was quantified using assumptions on standard portion sizes²⁸ and divided into 5 categories, 0 to 3, >3 to 10, >10 to 20, >20 to 30, and >30 g/d. The lowest intake group was defined to include a group with a very low intake, allowing for occasional intake only (0–3 g/d); other groups corresponded with fish consumed as a hot meal twice a month, once a week, more than once but less than twice a week, and twice a week or more often, respectively.

Dietary Intake of LCN3FAs Based on the FFQ

Intake of LCN3FAs was quantified based on estimated fish intake and the Danish food composition tables.²⁹ We energy-adjusted the estimated intake of LCN3FAs by the residual method to separate any

effect of LCN3FAs from the effect of total energy intake and to reduce extraneous variation in intake of LCN3FAs.³⁰ The residual method calculates the residuals from regressing “log(nutrient)” on “log(energy)” and adds the expected nutrient intake associated with an average energy intake. The lowest 3% with respect to energy-adjusted intake of LCN3FAs were evaluated as a “very-low intake group,” and the remaining sample was divided into quintiles. These exposure groups were decided on a priori to enable us to investigate any possible effects in a very low intake group (the lowest 3%) but to still have a relatively large comparison group (the highest quintile).

Consistently Reported Fish Intake on 3 Different Measurement Occasions

Women reporting the same frequency of fish intake in both telephone interviews and the FFQ were grouped into fish intake frequency levels as follows: (1) 0; (2) less than once a month; (3) each month; and (4) each week. This categorization resulted in a marked restriction of the study sample but was chosen to reduce the nondifferential misclassification, which must be expected when self-reported dietary intakes are applied. In supplementary analyses, we also used fish intake averaged across all 3 of the assessment occasions and quintiles of LCN3FA intake as exposures, respectively.

Outcome

We obtained information on all of the admissions to hospital among participants from the Danish National Patient Registry. The National Patient Registry contains information on all hospitalizations in Denmark since 1977.³¹ We assessed diagnosis of cerebrovascular diseases (International Classification of Diagnosis system [ICD] 10 codes I60–69 and ICD-8 codes 430–438), ischemic heart diseases (ICD-10 codes I20–25 and ICD-8 codes 410–414), and hypertensive diseases (ICD-10 codes I10–15 and ICD-8 codes 400–404). An event of cardiovascular disease was defined as a woman admitted to the hospital with one of the diagnoses listed above, after terminating the pregnancy, with which she entered the study population, and before the end of follow-up, which was September 1, 2008. According to the Danish Register of Causes of Death, there were 5 cardiovascular deaths without previous diagnosis of cardiovascular disease in the study population during the follow-up period. These were included in our analyses as fatal cases of cardiovascular disease.

In supplementary analyses we investigated the associations between LCN3FA intake and each of the end points, cerebrovascular, hypertensive, and ischemic heart disease, separately. Furthermore, we discerned among inpatient, outpatient, and emergency department contacts, and we used information on all of the diagnoses of cardiovascular disease before pregnancy.

Covariates

From the telephone interviews, we gathered information on age, parity (nulliparous or parous), prepregnancy body mass index (<18.5, $\geq$ 18.5–25.0, $\geq$ 25.0–30.0, and $\geq$ 30.0), cohabitation (single or cohabiting), occupation (white collar, skilled, unskilled, student, or unemployed), school ($\leq$ 10 years, high school, or unknown), smoking early in pregnancy (nonsmoking, occasionally, or daily), alcohol intake before pregnancy (0, >0–7, >7–14, or >14 drinks per week), leisure time physical activity in pregnancy (no or yes), and from the FFQ we used information on intake of saturated fat, dietary fiber, and *trans*-fatty acids in quintiles, as well as total energy intake.

Statistical Analyses

A total of 63 276 women in the DNBC filled in the FFQ. Because women could be enrolled in the DNBC more than once, with subsequent pregnancies, we used data from the first singleton pregnancy each woman contributed to the cohort (n=61 409). We excluded women who reported taking fish oil as a supplement during

Table 1. Characteristics of Participants in the Danish National Birth Cohort and Cardiovascular Disease (CVD) (N=48 627)

Characteristics	Overall		Fish Intake, g/d						CVD		
	N	%*	0–3	3–10	10–20	20–30	30+	P†	CVD	No CVD	P†
Age at enrollment, %‡											
<25 y	6391	13	23	17	13	10	9	<0.0001	9	13	<0.0001
≥25–35 y	37 123	76	71	76	77	78	77		70	76	
≥35 y	5113	11	7	8	10	12	15		21	10	
Nulliparous, %‡	25 389	52	58	54	53	49	50	<0.0001	38	52	<0.0001
Single/unmarried, %‡	872	2	3	2	2	1	2	<0.0001	3	2	0.14
Daily smokers in pregnancy, %‡	5869	12	19	14	11	10	10		16	12	0.008
Alcohol before pregnancy, %‡											
No alcohol	5537	11	18	14	10	10	9	<0.0001	16	11	0.002
>0–7 drinks per wk	38 136	78	75	78	79	79	79		75	78	
>7–14 drinks per wk	4288	9	6	7	9	10	11		9	9	
>14 drinks per wk	666	1	1	1	1	1	2		1	1	
Prepregnant body mass index, %‡											
<18.5	2113	4	4	4	4	4	5	<0.0001	4	4	<0.0001
≥18.5–25.0	33 793	69	64	66	70	72	74		60	70	
≥25.0–30.0	9237	19	22	21	19	18	16		23	19	
≥30.0	3484	7	11	9	7	6	5		13	7	
School, %‡											
≤10 y school	11 671	24	33	30	24	20	18	<0.0001	30	24	0.001
High school	24 723	51	40	45	52	55	56		45	51	
Unknown	12 233	25	27	25	24	25	26		25	25	
Physically active in pregnancy, %‡	19 014	39	33	35	39	41	45	<0.0001	36	39	0.09
Occupation, %‡											
White collar	18 759	39	27	33	39	44	45	<0.0001	34	39	0.0001
Skilled	9190	19	20	21	20	18	15		20	19	
Unskilled	10 240	21	28	25	21	17	16		26	21	
Student	5633	12	12	10	11	12	13		8	12	
Unemployed	4805	10	14	11	9	9	10		13	10	

CVD indicates cardiovascular disease.

*Data show the percentage (columns) of women distributed by covariate.

†Data show the 2-sided *P* value from χ^2 test for measure of association.

‡Data show the percentage (columns) of women within fish intake or CVD group (except for row N, which is total No. of observations).

pregnancy (n=3180). This was done to avoid the analytic difficulties of distinguishing between effects of food- and supplement-derived nutrients, because we were not able to quantify intake of LCn3FAs from supplements.

Preeclampsia and gestational diabetes have been found previously to be closely related to subsequent cardiovascular disease; furthermore, women experiencing these complications are often encouraged by health professionals to change their diet during pregnancy. Hence, diet measured during pregnancy might not be a valid representation of these women's habitual dietary intake, and they were excluded (n=2573). Complete case analysis was applied (frequency of missing data range: 0–5.8%; n=5354), and, finally, questionnaires with a total energy intake <4200 kJ or >16 700 kJ were excluded (n=1675). Data from 48 627 women were included in our analyses, and women entering our final study population were similar to those who were excluded regarding age, parity, education, occupation, and smoking.

Kaplan-Meier estimates of the survivor functions were investigated to characterize the effect of exposure. We used Cox regression models to investigate the risk of cardiovascular disease associated with different levels of fish or LCn3FA intake, adjusting for joint confounding by including the covariates listed above in the models

along with the exposure variable. This method allows us to estimate the hazard ratio (HR) and associated 95% CIs. Investigation of the cumulative residuals did not reveal any violations to the assumption of proportional hazards. Age was used as the underlying time scale, and delayed entry was applied to account for the fact that women entered the cohort at different ages. Participants were, thus, considered at risk from their age at the time when they filled in the FFQ until the age at cardiovascular disease diagnosis, fatal cardiovascular disease, death, or the defined end of follow-up, whichever came first. Trend tests were performed by assigning the median intake to each exposure level and include this in the model as a continuous variable. All of the analyses were carried out using SAS statistical software (version 9, SAS Institute, Cary, NC).

Results

Characteristics of the study participants are given in Table 1. During the 6 to 12 years (median: 8 years) of follow-up from 1996 to 2008, 577 events of cardiovascular disease were identified. Of these, 328 were events of hypertensive disease, 146 were events of cerebrovascular disease, and 103 were

Table 2. Fish Intake, Intake of Long-Chain n-3 Polyunsaturated Fatty Acids and Risk of Cardiovascular Disease (N=48 627)

				Cardiovascular Disease			
Exposure	N	%	No. of Cases	Crude		Adjusted*	
				HR	95% CI	HR	95% CI
Fish intake g/d							
0–3	4452	9	71	1.78	1.32–2.42	1.54	1.13–2.11
>3–10	10 731	22	129	1.24	0.95–1.60	1.12	0.86–1.46
>10–20	15 771	32	173	1.05	0.82–1.34	1.01	0.79–1.29
>20–30	8527	18	98	1.02	0.78–1.34	1.01	0.77–1.34
>30	9146	19	106	Ref	...	Ref	...
					<i>P</i> =0.0008†		<i>P</i> =0.038†
					<i>P</i> =0.003‡		<i>P</i> =0.024‡
LCn3FA intake (median g/d)							
Lowest 3% (0.06)	1446	3	29	2.18	1.44–3.30	1.91	1.26–2.89
First quintile (0.13)	9227	19	122	1.41	1.08–1.83	1.26	0.96–1.65
Second quintile (0.21)	9521	20	113	1.21	0.92–1.58	1.12	0.85–1.47
Third quintile (0.31)	9517	20	99	1.04	0.78–1.37	1.00	0.76–1.33
Fourth quintile (0.45)	9509	20	115	1.17	0.90–1.53	1.16	0.89–1.52
Fifth quintile (0.73)	9407	19	99	Ref	...	Ref	...
					<i>P</i> =0.002†		<i>P</i> =0.035†
					<i>P</i> =0.003‡		<i>P</i> =0.023‡

LCn3FA indicates long-chain n-3 polyunsaturated fatty acid; Ref, reference; HR, hazard ratio.

*Data were adjusted for physical activity, prepregnant body mass index, smoking, school, cohabitant status, parity, occupation, prepregnant alcohol intake, total energy intake, intake of saturated fat, dietary fiber, and *trans*-fatty acids.

†Data show overall χ^2 test of effects.

‡Data show test for trend.

events of ischemic heart disease. Women with a low fish intake were more likely to be <25 years at enrollment, nulliparous, smokers, overweight/obese, and less likely to have attended high school, to be white collar workers, to drink alcohol, and to be physically active compared with women with a high fish intake.

The following Tables 2 and 3 show the number of women with cardiovascular disease according to exposure, as well as crude and adjusted HR for cardiovascular disease, with women in the highest exposure groups as the reference category.

In Table 2, the exposure measures were fish and LCN3FA intake measured at 1 time point by the FFQ. Study participants in the lowest fish intake group had an elevated risk of cardiovascular disease compared with women in the highest fish intake group (crude HR: 1.78 [95% CI: 1.32–2.42], adjusted HR: 1.54 [95% CI: 1.13–2.11]). For intermediate groups, risk estimates were close to 1, and CIs included unity. With respect to intake of LCN3FAs, results were similar but with a higher risk estimate for the lowest intake group (crude HR: 2.18 [95% CI: 1.44–3.30]; adjusted HR: 1.91 [95% CI: 1.26–2.89]). This is also illustrated in the Figure, which shows the Kaplan-Meier curves with respect to cardiovascular disease stratified on LCN3FA intake groups.

Table 3 shows the risk of cardiovascular disease in a subset of women who consistently reported the same fish intake in each trimester. Again, the same pattern is seen; risk of

cardiovascular disease was ≈ 3 times higher for women who never ate fish compared with women who ate fish every week (crude HR: 3.76 [95% CI: 1.94–7.30]; adjusted HR: 2.89 [95% CI: 1.39–5.99]).

The analyses presented in Tables 2 and 3 also show an overall difference in risk of cardiovascular disease between exposure groups, as well as a trend in disease risk, when exposure groups were treated as a continuous variable.

The results from the supplementary analyses treating each of the 3 end points (cerebrovascular, hypertensive, and ischemic heart disease) as separate outcome measures showed an increased risk for the lowest intake group for all 3 of the end points. HRs for lowest versus highest LCN3FA intake group were 1.81 (95% CI: 1.03–3.19), 2.34 (95% CI: 1.10–4.99), and 3.80 (95% CI: 1.53–9.42) for hypertensive, cerebrovascular, and ischemic heart disease, respectively.

Discussion

In a large prospective cohort of women, we found that low intake of fish or LCN3FAs was associated with an elevated risk of cardiovascular disease. No increase in risk was observed for modest fish or LCN3FA intake. In a subset of women who consistently reported the same frequency of fish intake on 3 different measurement occasions during a period of 30 weeks, we saw an ≈ 3 -fold higher disease risk for

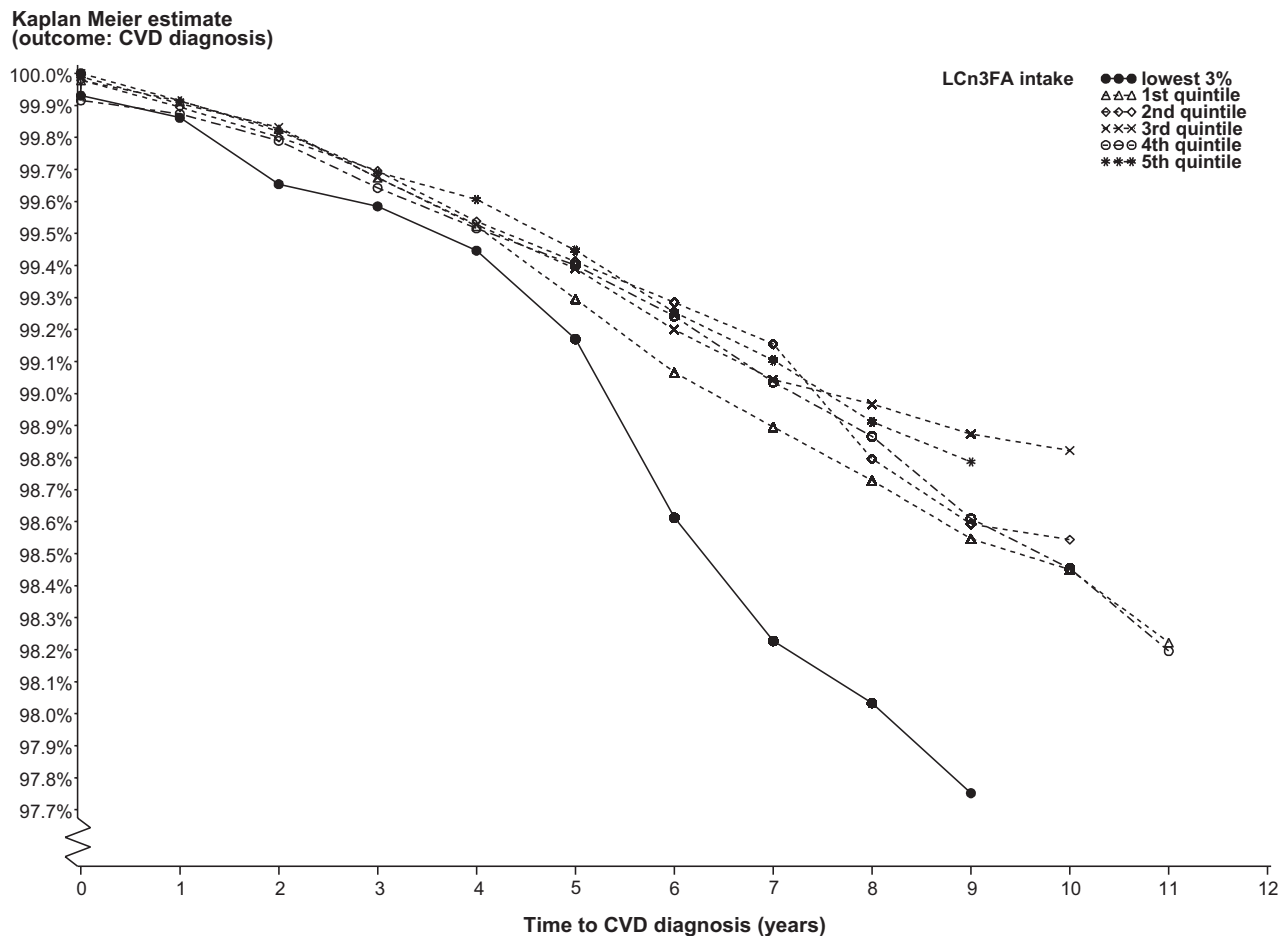


Figure. Cardiovascular disease curves by Kaplan-Meier estimates for the 5 different LCn3FA intake groups. CVD indicates cardiovascular disease; LCn3FA, long chain n-3 polyunsaturated fatty acid.

women who never ate fish compared with women consuming fish every week.

Participants in the DNBC were relatively young and healthy at enrollment. The demographic characteristics and the composite outcome definition in our study might complicate comparison with other studies in the field.

In addition to the randomized, controlled trials, which, for the most part, are secondary prevention trials conducted in

men,^{6–8,32} observational prospective studies have also shown fish consumption and LCn3FAs in varying amounts to be inversely associated with fatal coronary heart disease.^{1–5} In some studies no such association has been observed,^{33–35} or an association has been seen for some but not for other cardiovascular outcomes.³⁶

Based on our English-language Medline search through October 2010, it is apparent that only a few studies have been

Table 3. Consistently Reported Fish Intake and Risk of Cardiovascular Disease (N=6066)

Fish Intake Frequency (Median LCn3FA Intake, g/d)	N	%	No. of Cases	Cardiovascular Disease			
				Crude		Adjusted*	
				HR	95% CI	HR	95% CI
Never (0.10)	387	6	11	3.76	1.94–7.30	2.89	1.39–5.99
Less than each mo (0.14)	165	3	2	1.43	0.35–5.88	0.87	0.20–3.74
Each mo (0.20)	949	16	10	1.11	0.56–2.19	0.96	0.47–1.95
Each wk (0.60)	4565	75	53	Ref	...	Ref	...
					<i>P</i> =0.001†		<i>P</i> =0.027†
					<i>P</i> =0.0004‡		<i>P</i> =0.018‡

LCn3FA indicates long-chain n-3 polyunsaturated fatty acid; Ref, reference; HR, hazard ratio.
*Data were adjusted for physical activity, prepregnant body mass index, smoking, school, cohabitant status, parity, occupation, prepregnant alcohol intake, total energy intake, intake of saturated fat, dietary fiber, and *trans*-fatty acids.
†Data show overall χ^2 test of effects.
‡Data show test for trend.

conducted in female study populations. Another recent Danish follow-up study including middle-aged men and women showed an inverse association between intake of fatty fish and risk of acute coronary syndrome in men but no association in women.³⁷ This might be because of a lower number of observations and events compared with our study but could also be caused by the lack of an exposure group with only occasional fish intake. Our findings were consistent with results from another large observational prospective cohort of women, the Nurses' Health Study, where intake of fish and LCN3FAs was found to be inversely associated with risk of coronary heart disease³⁸ and thrombotic infarction.³⁹ As in our study, differences were primarily observed between the very lowest intake group and the others. Furthermore, in the study examining risk of coronary heart disease, findings were stronger for fatal than for nonfatal outcomes. Because our study population was much younger (mean age at follow-up was <40 years) we observed few fatal cases of cardiovascular disease. Allowing for a longer follow-up period might have strengthened our findings.

The biological properties of LCN3FAs and the pathophysiology of cardiovascular diseases make the idea of a protective effect of fish consumption probable. Physiological effects of intake of LCN3FAs include altered cell membrane fluidity and receptor responses after incorporation of LCN3FAs into cell membrane phospholipids,^{40,41} as well as direct binding of LCN3FAs to cytosolic receptors that regulate gene transcription⁴² and complex interactions with ion channels.⁴³ These mechanisms have varying dose responses and time responses of effect.¹² Apparent discrepancies in the results of previous studies might thus reflect the different responses of effect depending on the chosen outcome measure, as well as differences in levels of habitual intake across study populations.

In our study, an effect of intake of fish or LCN3FAs was seen only for the lowest intake group. This could indicate a potential threshold effect of fish consumption, as has been shown in meta-analyses.^{44,45} However, CIs for several of the exposure categories in our analyses were broad, and, therefore, an elevated risk in some of the intermediate categories compared with the highest intake category cannot be excluded.

The major strengths of our study include its large size, prospective design, and the detailed information on fish intake during pregnancy, enabling us to focus on a restricted study sample, who consistently reported the same frequency of fish intake through pregnancy. By applying these strict criteria we believe that we removed some of the random noise inherent in each of the self-reported measures and, thus, obtained a more valid measure of the habitual fish intake of the participants. Furthermore, previous analyses within the DNBC have shown reasonably good correlation between intake of LCN3FAs estimated from the FFQ and LCN3FAs quantified in erythrocyte lipids (unpublished results).

In secondary analyses we used fish intake averaged across the 3 dietary assessment occasions as our exposure, and we looked at LCN3FAs in quintiles as exposure. In both cases the results were consistent with our primary findings.

Other studies, as well as previous analyses within the DNBC,⁴⁶ have shown fish intake to be strongly correlated with sociodemographic and behavioral characteristics, including smoking. We adjusted for a wide range of potential confounders in our analyses, and although the associations between intake of fish and LCN3FAs were attenuated upon adjustment, they remained statistically significant. A possible explanation for our findings might be that the elevated risk of cardiovascular disease observed for the lowest intake group reflected residual confounding. For some of the exposures, such as physical activity and smoking, data were only collected during pregnancy. Women may alter their activity patterns during pregnancy, and the fact that we were not able to adjust for long-term activity levels might have resulted in residual confounding. However, we find it reassuring for interpreting our results as a true effect of LCN3FA intake that the associations were strongest when we applied the strict criteria of consistently reported fish intake across all 3 of the measurements despite a marked reduction in the sample size.

The validity of the diagnosis of acute myocardial infarction in the National Patient Registry has been examined and found to be relatively good,⁴⁷ but we used a broader range of cardiovascular diagnoses for our outcome because of the low incidence of cardiovascular disease in our young study population. This is not unproblematic, because hypertension is itself a risk factor or an intermediate variable of atherosclerosis. However, supplementary analyses treating hypertensive, cerebrovascular, and ischemic heart disease as separate end points showed patterns of association similar to the primary analyses and indicated that the effect might be strongest for ischemic heart disease. Incorporation of LCN3FAs into atherosclerotic plaques has been shown to have a plaque-stabilizing effect,⁴⁸ which might represent an important mechanism by which LCN3FAs could reduce the risk of ischemic heart diseases. The results of our analyses treating the 3 end points separately thus support the biological plausibility of our findings and are reassuring with respect to the composite cardiovascular outcome measure in our study.

In additional analyses we also excluded all of the previous cases of cardiovascular disease (165 previous cases) and all of the emergency department or outpatient contacts, respectively, but estimates remained largely unaltered. We also conducted a sensitivity analysis where women who had experienced preeclampsia or gestational diabetes were included in the study population, which attenuated the effect estimates but did not change our conclusions, and adjusted HR for lowest versus highest LCN3FA intake group was 1.54 (95% CI: 1.04–2.28).

Perspectives

Findings from this large prospective study based on relatively young and initially healthy women indicate that no or a very low intake of fish and LCN3FAs is associated with an increased risk of cardiovascular disease. Our results are in line with previous observational studies based on older women that suggest that the potential beneficial effect is seen with relatively moderate intakes compared with little or no fish intake.

Acknowledgments

We acknowledge the contributions of the managerial team of the Danish National Birth Cohort. We also acknowledge the bodies funding the Danish National Birth Cohort: the March of Dimes Birth Defects Foundation, Danish Heart Association, Danish Medical Research Council, Sygekassernes Helsefond, Danish National Research Foundation, Danish Pharmaceutical Association, Ministry of Health, National Board of Health, and Statens Serum Institut. We also acknowledge the Centre for Fetal Programming (CFP). CFP is supported by the Danish Council for Strategic Research (grant 09-067124).

Sources of Funding

This study was supported by the Faroese Research Council, the Fisheries Research Fund of the Faroe Islands, the European Union sixth framework programme Integrated Research Project SEAFOOD-plus (FOOD-CY-2004-506359), the European Union sixth framework programme EARNEST (FOOD-CT-2005-007036), and the Nordic Working Group on Fishery Research.

Disclosures

None.

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Hypertension. 2012;59:36-43; originally published online December 5, 2011;
doi: 10.1161/HYPERTENSIONAHA.111.179382

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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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