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Adipose Tissue Content of Marine N-3 Polyunsaturated Fatty Acids Is Inversely Associated With Myocardial Infarction

Several, but not all, cohort studies have reported an inverse relationship between intake of marine n-3 polyunsaturated fatty acids (PUFA) and coronary heart disease (CHD) (1). Most epidemiological studies have assessed the intake of n-3 PUFA using questionnaires, but interestingly, biomarker studies have more consistently reported an inverse association of n-3 PUFA with CHD. In particular, adipose tissue marine n-3 PUFA has been suggested as an appropriate biomarker, as it reflects intake and metabolism during the past 1 to 2 years (1).

The Danish Diet, Cancer, and Health study is a cohort study previously described in detail (2). Briefly, 57,053 subjects between 50 and 65 years of age were enrolled between 1993 and 1997 and followed until July 2013. For this study, we used a case-cohort design including cases of myocardial infarction (MI) and a randomly selected subcohort (n = 3,500). We identified all participants in the cohort registered with an incident diagnosis of MI in the Danish National Patient Registry and/or the Danish Causes of Death Registry, according to the International Classification of Disease coding. Furthermore, cases of cardiac arrest were included if they were considered to be of cardiac origin after validation. At baseline, each participant filled in a detailed questionnaire on diet, life-style, and medical history. Blood samples were drawn, and an adipose tissue biopsy was collected from the buttocks, as previously described (3). The composition of fatty acids in adipose tissue was determined by gas chromatography, and results were expressed as weight percent of total fatty acids (3). Measures of association were assessed using Cox proportional hazards models with age as the time axis. We used a weighting scheme to account for the size of the subcohort. Potential confounders were selected a priori, and the proportional hazards assumption was checked, with no significant violations. Data were analyzed using STATA version 13.1 (StataCorp LP, College Station, Texas). The study was conducted according to the Helsinki Declaration and was approved by the regional ethics committees.

We identified 3,089 cases of incident MI during a median follow-up of 17 years. The subcohort resembled the entire cohort on all baseline parameters. We excluded subjects for whom information regarding covariates used in the adjusted analyses was missing (n = 643) and a further 421 subjects (214 cases and 207 subcohort) because of missing data regarding adipose tissue composition, leaving 2,814 cases and 3,163 participants from the subcohort for evaluation.

The associations of marine n-3 PUFA (eicosapentaenoic acid [EPA], docosahexaenoic acid [DHA] and docosapentaenoic acid [DPA]) in adipose tissue with incident MI are given in **Table 1**. Results for model A were adjusted for traditional risk factors for CHD and medical disorders, whereas model B included adjustment for traditional risk factors and dietary variables. We found an inverse association of adipose tissue content of EPA and DHA with incident MI. When comparing the highest and lowest quintile, hazard ratios of 0.76 (95% confidence interval: 0.63 to 0.91) and 0.78 (95% confidence interval: 0.64 to 0.95) were found for EPA and DHA, respectively. The associations were rather similar between models. Conversely, DPA was positively associated with MI

TABLE 1 Adipose Tissue Content of Marine n-3 PUFA and Association With Myocardial Infarction

	Model A*	Model B†
Content of EPA, %		
Q1 (0.00–0.07)	1.00	1.00
Q2 (>0.07–0.09)	0.98 (0.82–1.17)	0.93 (0.78–1.11)
Q3 (>0.09–0.11)	0.83 (0.69–1.00)	0.77 (0.63–0.93)
Q4 (>0.11–0.13)	0.92 (0.76–1.11)	0.84 (0.68–1.04)
Q5 (>0.13)	0.76 (0.63–0.91)	0.64 (0.50–0.82)
Content of DPA, %		
Q1 (0.00–0.21)	1.00	1.00
Q2 (>0.21–0.25)	1.21 (1.01–1.45)	1.26 (1.05–1.51)
Q3 (>0.25–0.29)	1.11 (0.91–1.36)	1.21 (0.97–1.50)
Q4 (>0.29–0.34)	1.11 (0.92–1.34)	1.26 (1.02–1.56)
Q5 (>0.34)	1.15 (0.94–1.40)	1.40 (1.08–1.80)
Content of DHA, %		
Q1 (0.00–0.18)	1.00	1.00
Q2 (>0.18–0.23)	0.93 (0.77–1.12)	0.91 (0.75–1.09)
Q3 (>0.23–0.29)	0.91 (0.75–1.09)	0.87 (0.71–1.05)
Q4 (>0.29–0.37)	0.97 (0.81–1.17)	0.88 (0.72–1.08)
Q5 (>0.37)	0.78 (0.64–0.95)	0.72 (0.56–0.94)

Values are hazard ratios (95% confidence intervals) from the Cox proportional hazards model. *Adjusted for traditional risk factors including: smoking, body mass index, waist circumference, physical activity, alcohol intake, educational level, and additionally, medical history of diabetes mellitus, hypertension, and hypercholesterolemia. †Adjusted for traditional risk factors and dietary variables: adipose tissue content of total saturated, monounsaturated and polyunsaturated (excluding marine n-3 PUFA) fatty acids and dietary fiber.

DHA = docosahexaenoic acid; DPA = docosapentaenoic acid; EPA = eicosapentaenoic acid; PUFA = polyunsaturated fatty acids; Q = quintile.

when comparing the highest to the lowest quintile, although this was only statistically significant for model B. Pearson's correlations coefficients with dietary intake of the corresponding n-3 PUFA were modest for EPA ($r = 0.36$; $p < 0.001$) and DHA ($r = 0.34$; $p < 0.001$) and weak for DPA ($r = 0.08$; $p = 0.001$).

This study had limitations. The median follow-up was 17.0 years, and dietary measures were not assessed further during the study period. A long follow-up allowed us to accumulate more outcome events, but subjects might change their diet over time. Furthermore, changes in medical care and lifestyle together with public awareness of disease prevention might influence the participants' risk over time. To address this issue we performed supplementary analysis stratifying on the birthdate and tested for interaction from birthdate. No significant interaction was detected.

Several mechanisms have been suggested to explain cardioprotective properties of marine n-3 PUFA, including stabilization of atherosclerotic plaques, which may decrease the risk of plaque rupture and MI (1). The mechanism(s) by which n-3 PUFA interact with the risk of MI in the present study are uncertain, but the results suggest that EPA and DHA play a more important role than DPA. In conclusion, the study supports the view that marine n-3 PUFA may protect against MI.

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The Need for Comprehensive Cardiac Catheterization in Children With Pulmonary Hypertension

We read with interest the paper by O'Byrne et al. (1) on adverse events during cardiac catheterization in children with pulmonary hypertension (PH). However, we are concerned about the effect that this paper may have on patients, family members, and health care providers and on the future clinical care of children with PH. The presented data are based on a chart review of catheterizations performed in both expert and nonexpert centers (the Pediatric Health Information System database) in children with PH of multiple etiologies and settings (acute, perioperative, and chronic). We are concerned about the possible interpretation that children with PH should not undergo cardiac catheterization because of the risks of severe adverse events; such misleading views may counteract the recent efforts of many experts to standardize diagnostic work-up and care in pediatric PH (2,3).

First, exact diagnosis, oxygen saturation, hemodynamics, and laboratory and imaging data were not available to characterize the PHIS population (1) any better. Second, the PH subclassification used was limited and was not in line with the current PH classification (2). Third, O'Byrne et al. (1) included perioperative PH and interventional catheterizations, and thus mixed moderate- with high-risk patients, thereby increasing bias and decreasing validity. Moreover, in cardiomyopathies and structural heart disease, PH hemodynamics and physiology can differ remarkably (e.g., children with a right ventricular decompressing shunt have better outcomes), but were not analyzed separately.

Robust data on the safety of cardiac catheterization in pediatric PH comes from the TOPP (Tracking Outcome and Practice in Pediatric Pulmonary Hypertension) registry: for the total number of cardiac catheterizations ($n = 908$), pulmonary hypertensive crises, need for inotropic support, and/or cardiac arrest were reported in 5.9%, and this included