Nutrition, Metabolism & Cardiovascular Diseases (2015) **25**, 1016–1024

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

Intake of polyunsaturated fat in relation to mortality among statin users and non-users in the Southern Community Cohort Study

J.N. Kiage [a,1], U.K.A. Sampson [b], L. Lipworth [a,c], S. Fazio [d], G.A. Mensah [b], Q. Yu [e], H. Munro [f], E.A. Akwo [a,c], Q. Dai [a], W.J. Blot [a,f], E.K. Kabagambe [a,c,*]

[a] *Division of Epidemiology, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN 37203, USA*
[b] *Center for Translation Research and Implementation Science (CTRIS), National Heart, Lung, and Blood Institute, Bethesda, MD 30105, USA*
[c] *Vanderbilt Center for Translational and Clinical Cardiovascular Research, Vanderbilt University Medical Center, Nashville, TN 37203, USA*
[d] *The Knight Cardiovascular Institute, Center for Preventive Cardiology, Oregon Health and Science University, Portland, OR 97239, USA*
[e] *Westat, Rockville, MD 20850, USA*
[f] *The International Epidemiology Institute, Rockville, MD 20850, USA*

Received 23 April 2015; received in revised form 17 July 2015; accepted 20 July 2015
Available online 29 July 2015

KEYWORDS
PUFA;
Fish;
Hypertension;
Mortality;
Cardiovascular disease;
Prospective

Abstract *Background and aims:* Consumption of polyunsaturated fatty acids (PUFA), especially the n3-series, may protect against cardiovascular disease (CVD), but recent randomized studies have failed to demonstrate these benefits. One of the prevailing hypotheses is that PUFA intake may not confer benefits beyond those provided by statins, but studies comparing statin users to non-users with regard to effects of PUFA are lacking.
Methods and results: Black and white men and women (n = 69,559) in the Southern Community Cohort Study were studied. Cox regression models adjusting for age, sex, race, BMI, recruitment site, education, income, smoking, diabetes, and dietary variables were used.
Results: At baseline the mean ± SD age was 52 ± 9 years, 60% of participants were women, 54% had hypertension and 16% used statins. We observed modest inverse associations between n3-PUFA and n6-PUFA intake with mortality among non-statin users but not among statin users. In adjusted analyses, the HRs (95% CIs) for all-cause mortality (6,396 deaths over a median of 6.4 years) comparing the highest to the lowest quintile were 0.90 (0.82–1.00) for n3-PUFA and 0.80 (0.70–0.92) for n6-PUFA among non-statin users, whereas they were 1.06 (0.87–1.28) and 0.96 (0.78–1.19) for n3-PUFA and n6-PUFA, respectively, among statin users.
Conclusions: Our results suggest potential benefits of PUFA consumption on mortality which are only apparent in the absence of statin therapy. It seems prudent to consider the potential benefit of PUFA consumption in the primary prevention of CVD among patients who are not candidates for statin therapy but are at increased risk for CVD and mortality.

Abbreviations: MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; SCCS, Southern Community Cohort Study; SFA, saturated fatty acids.

* Corresponding author. Division of Epidemiology, Department of Medicine, Vanderbilt University, Nashville, TN 37203, USA. Tel.: +1 615 322 8033; fax: +1 615 343 5938.
E-mail addresses: kiagejn@gmail.com (J.N. Kiage), uchechukwu.sampson@nih.gov (U.K.A. Sampson), loren.lipworth@vanderbilt.edu (L. Lipworth), fazio@ohsu.edu (S. Fazio), george.mensah@nih.gov (G.A. Mensah), qiluyu@westat.com (Q. Yu), heather@iei.us (H. Munro), elvis.a.akwo@vanderbilt.edu (E.A. Akwo), qi.dai@vanderbilt.edu (Q. Dai), william.j.blot@vanderbilt.edu (W.J. Blot), edmond.kabagambe@vanderbilt.edu (E.K. Kabagambe).
[1] Current address: Department of Medicine, University of Tennessee Health Science Center, Memphis, TN, USA.

http://dx.doi.org/10.1016/j.numecd.2015.07.006
0939-4753/

Introduction

Numerous observational studies and clinical trials have shown an inverse association between the intake of polyunsaturated fatty acids (PUFA), especially long-chain n3-fatty acids from fish, and blood pressure, myocardial infarction, and cardiovascular and total mortality [1–4]. However, recent findings from large randomized controlled trials have failed to demonstrate cardiovascular benefits of PUFA [5–7]. It is conceivable that the substantial increase in use of statins, which in most studies lower CVD- and all-cause mortality [8,9] and may reduce the efficacy of n3-fatty acids [10], could in part explain these different results. In this regard, Bjorck et al. [11] showed a huge increase in the use of lipid-lowering medications (mainly statins) among patients with first acute myocardial infarction in Sweden (10% in 1994 to 90% in 2002). Similarly, using data from the National Health and Nutrition Examination Survey, Mann et al. [12] showed that the use of statins among adults with high LDL-C concentration in the United States (US) has nearly doubled (19.6% in 1999 to 35.6% in 2004). It is noteworthy that 86% of participants in the Alpha Omega trial that was initiated in 2002 [5] were on lipid-lowering medications, mainly statins, at baseline compared to only 5% in the GISSI-Prevenzione trial that was initiated a decade earlier [2,13].

Apart from their potent effects on lipids [14], statins have pleiotropic effects that contribute to their cardiovascular benefits, among them blood pressure reduction [15,16]. A meta-analysis by Strazzullo et al. [17] combining results from 20 clinical trials shows that use of statins is associated with reduced diastolic and systolic blood pressure [17]. More recently, Golomb et al. [18] showed a modest but significant reduction in both diastolic and systolic blood pressure among non-hypertensive participants after 9 months of follow-up. Concordant with a view held by the investigators of the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) study [6], we hypothesized that in the context of widespread use of statins, which substantially lower background cardiovascular risk, increased intake of PUFA does not confer additional cardiovascular benefit, or that any benefits would be small and difficult to detect using typical sample sizes in randomized studies. To test this hypothesis, we used data from the Southern Community Cohort Study (SCCS), a large cohort of black and white participants living in the southeastern USA.

Methods

The design and methods of the SCCS have been described in detail [19]. Briefly, between 2002 and 2009, more than 85,000 adults aged 40–79 years were recruited from Alabama, Arkansas, Florida, Georgia, Kentucky, Louisiana, Mississippi, North Carolina, South Carolina, Tennessee, Virginia and West Virginia. Most participants (86%) were recruited at community health centers (CHC) where they completed computer-assisted personal interviews, including an 89-item food frequency questionnaire (FFQ) (www.southerncommunitystudy.org), with the assistance of trained staff; the remaining 14% were recruited via mail-based sampling of the general population and they completed mailed questionnaires. The questionnaire ascertained information on demographic and anthropometric characteristics, diet, lifestyle, medical history and use of selected medications, including statins [9,20]. Estimates for PUFA (and other nutrient) intakes were calculated by utilizing sex- and race-specific nutrient databases derived from government food consumption surveys in the southern USA [21]. Except for the overall fish intake, methods of preparation and specific questions on how tuna fish was consumed (e.g., as salad or casserole), specific information on other types of fish was not collected. Data on mortality was ascertained through linkage with the Social Security Administration and the National Death Index. The questionnaire adopted for the study has been widely validated within the SCCS and other populations in the USA [19,21,22]. The length of follow-up was computed as the difference between date of enrollment and the time a participant died, was lost to follow-up or until December 31, 2011, whichever came first. The study was approved by the institutional review boards of Vanderbilt University and Meharry Medical College, and all participants gave written informed consent.

Definitions and covariates

The dependent variables for our study were self-reported hypertension (yes/no) at baseline and CVD- and all-cause mortality. The exposure variables were energy-adjusted total PUFA, n3-PUFA and n6-PUFA intake distributed into quintiles, and fish intake grouped according to frequency of intake and method of usual preparation. Thus, fish consumption (tuna, fried fish, broiled fish, total of fried and broiled fish, and total of tuna, fried and broiled fish) was modeled as <1 time/month, 1–3 times/month, 1–3 times/week or ≥ 4 times/week. The following covariates were considered: age, sex, race, body mass index (BMI), recruitment site (CHC, general population), education ($<$high school, high school/GED, some college, graduate), annual household income ($<\$15{,}000$, $\geq \$15{,}000$), smoking ($\geq 20$ cigarettes/day, <20 cigarettes/day, past smoker, never smoker), alcohol intake (current if alcohol was consumed in the last one year, past, never drinker), diabetes (yes, no), statin use (yes, no), total energy intake, and energy-adjusted intakes of saturated fatty acids (SFA), monounsaturated fatty acids (MUFA) and proteins.

Statistical analysis

To address the objectives of the current study, data from 69,559 participants were analyzed. Due to high correlations between total energy intake and macronutrient variables, we computed energy-adjusted PUFA, MUFA, SFA and protein variables by using the residual method [23,24]. One-way ANOVA (for continuous variables) and chi-square tests (for categorical variables) were used to test for the