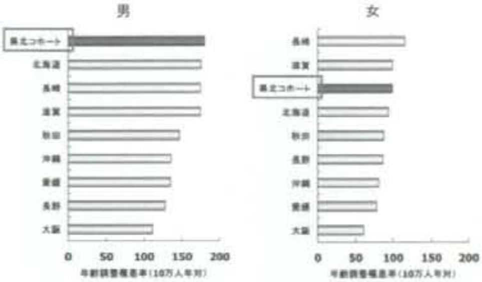
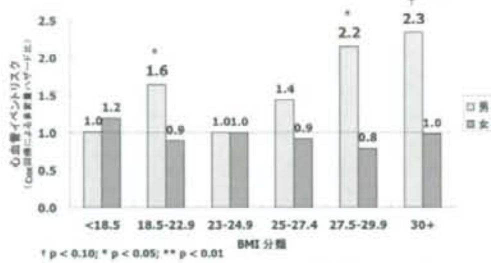
脳卒中発生率の他地域との比較



(県北コホート以外の地域の年齢調整罹患率は平成5年度厚生労働省循環器病研究委託費による研究報告集より作図)

太っている男性の心血管イベント(脳卒中・心筋梗塞)リスクは2倍高い



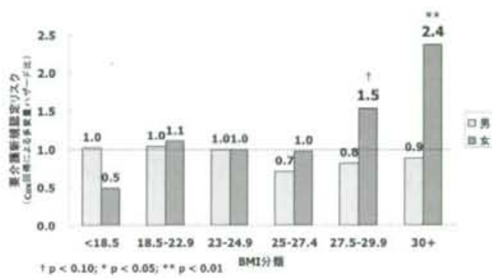
脳卒中、心筋梗塞の既往がなく、介護認定を受けていない65歳以上の男女

性別・年齢別の要介護新規認定率[§]

年齢階級	男			女		
	人年	認定数	認定率	人年	認定数	認定率
40-64	8,641	5	0.6	20,212	14	0.7
65-74	7,939	80	10.1	13,196	115	8.7
75+	2,959	90	30.4	3,677	128	34.8
総 数	22,590	175	8.6	42,918	257	6.6

[§]要支援以上に新規認定された者。ただし、脳卒中・心筋梗塞・心不全の既往者、介護認定を受けている者を除く。認定率は対1000人年(1年当たり人口1000人中の認定数)で表示

太っている女性は介護認定リスクが高い



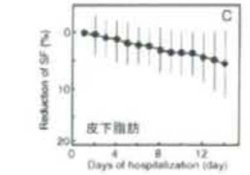
脳卒中、心筋梗塞の既往がなく、介護認定を受けていない65歳以上の男女

メタボリックシンドロームの治療

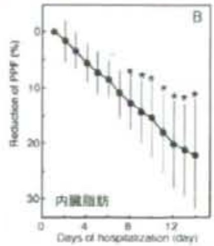
生活習慣の改善が第一

減量が第一

➢減量により減少する脂肪組織は内臓脂肪



高脂血症がある肥満者10人
(49.9歳, BMI=36.0 kg/m²)
入院による14日間の低カロリー食事療法
(1,000 kcal/日)



(Li Y, Exp Biol Med 228;1118,2003)

減量が第一

- 内臓脂肪の減少により善玉アディポサイトカイン（アディポネクチン）が増加

メタボリックシンドロームの治療

- 食事療法
- 運動療法
- 薬物療法

食事療法の3つの柱

- 摂取カロリーの制限
- 三大栄養素（炭水化物、脂質、蛋白質）の摂取割合の再調整
- 食行動の是正

摂取カロリーの制限

25-30kcal*kg標準体重 BMI22を標準体重とすると		
身長 (cm)	標準体重 (kg)	摂取カロリー
150	50	1500
155	53	1600
160	56	1700
165	59	1800
170	64	1900
175	67	2000

それでは、皆さんはドンだけ食っているか知ってますか？

男の人で 2500 kcal
女の人で 1800 kcal
食べています！

さて、主婦のBさんは1日にどのくらいカロリーを取っているでしょうか？

Bさんのプロフィール：
　女性　年齢55歳、兼業農家で主婦
　身長 153 cm、体重 65 kg、BMI 27.7
　血圧 140/85 mmHg、コレステロール 255 mg/dL、
　中性脂肪 185 mg/dL、HbA1c 5.8%

保健師からはカロリー制限を勧められました。
　理想体重は51 kg
　理想的な摂取カロリーは1500 kcal/日

さて、主婦のBさんは1日にどのくらいカロリーを取っているでしょうか？

朝　食：ご飯半分（131 kcal）、味噌汁（けんちん汁）（170 kcal）
　　卵2個で卵焼き（250 kcal）、サラダ（200 kcal）、
　　ほうれん草ソテー（55 kcal）、塩鮭（120 kcal）

昼　食：焼きうどん（540 kcal）、小松菜　ゴマ和え（55 kcal）、
　　かぼちゃそぼろあんかけ（140 kcal）、アロエヨーグルト（148 kcal）
午　後　缶コーヒーのジョージア1本（78 kcal）
　　シュークリーム（267 kcal）、バンホーテンミルクココア（91 kcal）

夕　食：ご飯半分（131 kcal）、味噌汁（とん汁）（170 kcal）、カニクリームコロッケ
　　（430 kcal）、酢豚（395 kcal）、アボガド1個（290 kcal）

朝：927 kcal　昼：883 kcal　午後：436 kcal　夕：1416 kcal
総計=3662 kcal（2162 kcalのオーバー）

さて、理想的なカロリー摂取を心がけるとどんな食事になるでしょうか？

朝　食：ご飯1杯（262 kcal）、味噌汁（具なし、ねぎのみ）（35 kcal）
　　あじ塩焼き（90 kcal）、かぶの漬け物（15 kcal）

昼　食：ご飯1杯（262 kcal）、中華風5目スープ（100 kcal）
　　麻婆豆腐（260 kcal）、春雨中華サラダ（120 kcal）
午　後　麦茶（0 kcal）

夕　食：ご飯1杯（262 kcal）、味噌汁（とん汁170 kcal）、サンマの塩焼き
　　（165 kcal）、大根おろし40g（8 kcal）、かぼちゃ50gの素揚げ（53 kcal）

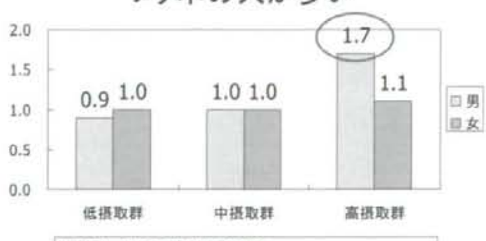
朝：402 kcal　昼：742 kcal　午後：0 kcal　夕：694 kcal
総計=1838 kcal（ごはんをすべて半分にすると1445 kcal）

三大栄養素とは

食品の種類		1単位（80 kcal）あたりの栄養素の平均含有量		
		炭水化物（g）	たんぱく質（g）	脂質（g）
主に炭水化物を含む食品		18	2	0
		20	0	0
主にたんぱく質を含む食品		0	9	5
		6	4	5
主に脂質を含む食品		0	0	9

（「糖尿病食事療法のための食品交換表　第6版」より作表）

炭水化物をたくさん摂っている人にメタボの人が多い



総カロリーに占める炭水化物の割合
低摂取群：40%以下、中摂取群：40-60%、高摂取群：60%以上

（Park YW. Arch Intern Med 163:427,2003）

脂肪酸の種類と代表的な食品

脂肪酸の種類	主な脂肪酸	主な食品
飽和脂肪酸	パルミチン酸、ステアリン酸など	ココナッツ、チョコレート、ナッツ、乳製品、動物脂
1価不飽和脂肪酸	オレイン酸など	オリーブオイル、菜種油、アボガド、ピーナッツ油
n-3系多価不飽和脂肪酸	α-リノレン酸	亜麻仁、大豆、胡桃、菜種油、紫蘇油、麻、かぼちゃ
	エイコサペンタエン酸（EPA）	魚、甲殻類
	ドコサヘキサエン酸（DHA）	魚、甲殻類
n-6系多価不飽和脂肪酸	リノール酸など	とうもろこし油、紅花油、ひまわり油、大豆、卵、赤身肉

（大澤正樹，2006）

脂肪の見分け方

飽和脂肪

冷蔵庫に入れると固まる油

脂身の多い肉・ベーコン・ソーセージ・ロースハム・チーズ・バター・油で揚げたインスタントラーメン・ポテトチップス・チョコレート・クッキー・ビスケット・ドーナッツ・ケーキ など

不飽和脂肪

冷蔵庫に入れても固まらない油

大豆油・菜種油・ごま油・豆腐・納豆・油揚げ・厚揚げ・魚介類・魚の卵 など

（メタボリックシンドローム予防の健康教育（拡大図版）より）

本日のまとめ

- 岩手県では他県より、脳卒中や心臓病で亡くなる方が多い。
- 岩手県北・沿岸地域の皆様は太っている人が多い。
- メタボリックシンドロームとは
  - 腹部肥満、血糖高め、血圧高め、脂質異常を重複して持っている状態です。
  - 心臓病や脳卒中の危険因子です。
- 治療は減量が第一です。食事の量と内容を点検しましょう。

Ⅳ．発症登録参加施設名・組織名及び研究協力者

研究参加施設名・組織名および研究協力者リスト

病院施設

岩手県立中央病院

院長　佐々木崇

脳神経センター長　関　博文

脳神経外科長　菅原孝行

神経内科長　高橋弘明

事務局長　吉田廣光

医事課長　鎌田隆一

盛岡赤十字病院

院長　沼里　進

脳神経外科部長　久保直彦

リハビリテーション科部長　木戸口順

神経内科部長　野崎有一

事務部長　佐々木利雄

岩手医科大学付属病院

院長　小林誠一郎

岩手県立二戸病院

院長　佐藤元昭

事務局長　照井善次

医事課長　山本康典

岩手県立久慈病院

院長　阿部　正

事務局長　高橋　仁

医事課長　松舘　隆

岩手県立一戸病院

院長　高田　耕

事務局長　菅原文芳

医事課長　小倉和彦

岩手県立軽米病院

院長　　　　　横島孝雄

事務局長　　　東山　昭

医事課長　　　中村善一

岩手県立宮古病院

院長　菅野千治

事務局長　菊池　儀

医事課長　菊池好徳

岩手県立二戸病院附属九戸地域診療センター

センター長　佐藤元昭

事務局長　　　小原鉄男

医事課　　　　高田こず恵

岩手県立山田病院

院長　　　　　及川修次

事務局長　　　小林岩松

済生会岩泉病院

院長　　　　　柴野良博

事務局長　　　佐々木嘉彦

国民健康保険種市病院

院長　　　　　漆久保潔

事務局長　　　苧坪健一

財団法人いわてリハビリテーションセンター

センター長　髙橋　明

栃内第二病院

院長　　　　　栃内秀彦

東八幡平病院

院長　　　　　及川忠人

南昌病院

院長　　　　　木村宗孝

盛岡繋温泉病院

院長　　　　　小西一樹

川久保病院

院長　　　　尾形文智

荻野病院

院長　　　　荻野忠良

保健所

二戸保健所、久慈保健所

所長　　　　田名場善明

宮古保健所

所長　　　　工藤淳子

市町村

二戸市、一戸町、軽米町、九戸村、久慈市、洋野町、野田村、普代村、宮古市、山田町、岩泉町、川井村、田野畑村

リサーチナース

岩手県立二戸病院担当

篠崎悦子、小野洋子、桜庭順子

岩手県立久慈病院担当

宇部ヤス子、藤森昭子

岩手県立中央病院担当

木戸口隆子、長澤郁子、平尾直美、工藤早由美

盛岡赤十字病院担当

狐崎妙子、中嶋京子、西本亜矢

岩手医科大学付属病院担当

増田妙子、井上弘子、遠藤愛子

Ｖ．研究成果の刊行に関する一覧表

1．学会発表

国内学会

小野田敏行，丹野高三，大澤正樹，板井一好，坂田清美，吉田雄樹，小川彰，石橋靖宏，田中文隆，中村元行，松舘宏樹，川村和子，岡山明．岩手県北地域住民の死亡率、循環器疾患罹患率および要介護認定率　岩手県北地域コホート研究より．第44回日本循環器病予防学会・日本循環器管理研究協議会総会，秋田、2008年5月．

栗林徹，丹野高三，大澤正樹，小野田敏行，板井一好，坂田清美，中村元行，岡山明．高齢女性の高度肥満は介護認定リスクを増加させる：岩手県北地域コホート研究．第67回日本公衆衛生学会、福岡市、2008年11月．

丹野高三，大澤正樹，小野田敏行，板井一好，八重樫由美，坂田清美，中村元行，小川彰，川村和子，栗林徹，松舘宏樹，岡山明．高齢者の不良な主観的健康感は介護認定リスクを増加させる：岩手県北地域コホート研究．第67回日本公衆衛生学会、福岡市、2008年11月

国際学会

Kozo Tanno, Masaki Ohsawa, Kazuyoshi Itai, Toshiyuki Onoda, Kiyomi Sakata, Motoyuki Nakamura, Akira Ogawa, Kuniaki Ogasawara, Yuki Yoshida, Kazuko Kawamura, Toru Kuribayashi, Akira Okayama. Poor self-rated health contributes to increased risk for stroke in Japanese elderly men. Joint Conference - 49th Cardiovascular Disease Epidemiology and Prevention -and- Nutrition, Physical Activity and Metabolism - 2009. March 11-14, 2009, Palm Harbor, Florida, USA.

Masaki Ohsawa, Karen Kato, Kazuyoshi Itai, Kozo Tanno, Yosuke Fujishima, Ryuichiro Konda, Motoyuki Nakamura, Toshiyuki Onoda, Kiyomi Sakata, Akira Okayama, Tomoaki Fujioka. Japanese hemodialysis patients have 9 to 20-fold higher mortality risks and 6 to 12-fold-higher incidence rates of stroke than those in normal controls Joint Conference - 49th Cardiovascular Disease Epidemiology and Prevention -and- Nutrition, Physical Activity and Metabolism - 2009. March 11-14, Palm Harbor, Florida, USA.

２．発表論文

Ohsawa M, Itai K, Onoda T, Tanno K, Sasaki S, Nakamura M, Ogawa A, Sakata K, Kawamura K, Kuribayashi T, Yoshida Y, Okayama. A Dietary intake of n-3 polyunsaturated fatty acids is inversely associated with CRP levels, especially among male smokers. Atherosclerosis 201 184-191, 2008.

Ohsawa M, Itai K, Tanno K, Onoda T, Ogawa A, Nakamura M, Kuribayashi T, Yoshida Y, Kawamura K, Sasaki S, Sakata K, Okayama A. Cardiovascular risk factors in the Japanese northeastern rural population. Int J Cardiol. 2008 Aug 14. [Epub ahead of print]

Makita S, Nakamura M, Satoh K, Tanaka F, Onoda T, Kawamura K, Ohsawa M, Tanno K, Itai K, Sakata K, Okayama A, Terayama Y, Yoshida Y, Ogawa A. Serum C-reactive protein levels can be used to predict future ischemic stroke and mortality in Japanese men from the general population.
Atherosclerosis. 2008 Aug 12. [Epub ahead of print]

Ⅵ. 研究成果の刊行物・別冊

ELSEVIER

Atherosclerosis 201 (2008) 184–191

ATHEROSCLEROSIS

www.elsevier.com/locate/atherosclerosis

Dietary intake of n-3 polyunsaturated fatty acids is inversely associated with CRP levels, especially among male smokers

Masaki Ohsawa[a,*], Kazuyoshi Itai[a], Toshiyuki Onoda[a], Kozo Tanno[a], Satoshi Sasaki[b], Motoyuki Nakamura[c], Akira Ogawa[d], Kiyomi Sakata[a], Kazuko Kawamura[e], Toru Kuribayashi[f], Yuki Yoshida[d], Akira Okayama[g]

[a] *Department of Hygiene and Preventive Medicine, School of Medicine, Iwate Medical University, Japan*
[b] *National Institute of Health and Nutrition, Japan*
[c] *Department of Medicine II, School of Medicine, Iwate Medical University, Japan*
[d] *Department of Neurosurgery, School of Medicine, Iwate Medical University, Japan*
[e] *Iwate Health Service Association, Japan*
[f] *Department of Health and Physical Education, Faculty of Education, Iwate University, Japan*
[g] *The First Institute of Health Service, Japan Anti-Tuberculosis Association, Japan*

Received 7 June 2007; received in revised form 27 January 2008; accepted 28 January 2008
Available online 17 March 2008

ELSEVIER

Atherosclerosis 201 (2008) 184–191

ATHEROSCLEROSIS

www.elsevier.com/locate/atherosclerosis

Dietary intake of n-3 polyunsaturated fatty acids is inversely associated with CRP levels, especially among male smokers

Masaki Ohsawa [a,*], Kazuyoshi Itai [a], Toshiyuki Onoda [a], Kozo Tanno [a], Satoshi Sasaki [b], Motoyuki Nakamura [c], Akira Ogawa [d], Kiyomi Sakata [a], Kazuko Kawamura [e], Toru Kuribayashi [f], Yuki Yoshida [d], Akira Okayama [g]

[a] *Department of Hygiene and Preventive Medicine, School of Medicine, Iwate Medical University, Japan*
[b] *National Institute of Health and Nutrition, Japan*
[c] *Department of Medicine II, School of Medicine, Iwate Medical University, Japan*
[d] *Department of Neurosurgery, School of Medicine, Iwate Medical University, Japan*
[e] *Iwate Health Service Association, Japan*
[f] *Department of Health and Physical Education, Faculty of Education, Iwate University, Japan*
[g] *The First Institute of Health Service, Japan Anti-Tuberculosis Association, Japan*

Received 7 June 2007; received in revised form 27 January 2008; accepted 28 January 2008
Available online 17 March 2008

Abstract

Objective: To examine whether dietary intake of n-3 polyunsaturated fatty acid (n-3PUFA) is associated with serum C-reactive protein (CRP) levels with regard to smoking status in the Japanese general population in a cross-sectional study.
Methods and results: A total of 14,191 participants aged 40–69 years were enrolled and divided into quartile groups according to their intake of n-3PUFA. Multivariate-adjusted logarithm-transformed CRP levels were compared between the quartile groups with regard to smoking status after adjusting for traditional risk factors and intake of saturated fatty acids. Adjusted CRP levels were inversely associated with dietary intake of n-3PUFA for both the male subjects and female subjects ($p < 0.05$ for trend). A linear trend was not seen between intake of n-3PUFA and adjusted CRP levels in male nonsmokers. Adjusted CRP level in the lowest quartile group of n-3PUFA was significantly higher than the levels in other groups in male smokers.
Conclusion: Sufficient dietary intake of n-3PUFA may attenuate inflammatory reaction and this effect is more evident among high-risk populations such as male smokers although the small numbers of female ex-smokers and nonsmokers limited statistical power to draw strong conclusions about these groups.

Keywords: n-3 Polyunsaturated fatty acid; C-reactive protein; Smoking; Nutrition; Risk factors

Accumulating evidence indicates that fish consumption is inversely correlated with fatal coronary artery disease and other atherosclerotic cardiovascular diseases (CVDs) [1,2]. However, the underlying biochemical mechanism has not been elucidated and the causal inference remains premature. n-3 Polyunsaturated fatty acids (n-3PUFA), which are contained in marine fish and some plants, play a key role in the prevention of CVD [3]. Possible mechanisms by which n-3PUFA lowers CVD mortality and morbidity are its effects on cardiac arrhythmia, hemodynamics, endothelial function, lipid metabolism, and coagulation function [4–8].

Chronic systemic inflammation plays a pivotal role in the development of atherosclerosis [9]. Traditional risk factors for atherosclerotic CVDs are thought to induce an inflammatory reaction and cause the development of atherosclerosis [9,10]. Cigarette smoking is considered a major factor responsible for the promotion and progression of atherosclerosis

* Corresponding author at: Department of Hygiene and Preventive Medicine, Iwate Medical University, 19-1 Uchimaru, Morioka 020-8505, Japan. Tel.: +81 19 651 5111; fax: +81 19 623 8870.
E-mail address: masakio@iwate-med.ac.jp (M. Ohsawa).

0021-9150/$ – see front matter © 2008 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.atherosclerosis.2008.01.008

[11,12], and smoking is also thought to induce inflammatory responses [13–15].

n-3PUFA is a precursor of anti-inflammatory eicosanoids, and the anti-inflammatory effects of n-3PUFA may play a key role in the prevention of CVDs. Favorable effects due to the dietary intake of fish with regard to preventing CVD are also evident, especially in high-risk populations, including smokers [1,2,16,17]. This evidence suggests that the anti-inflammatory effects of n-3PUFA attenuate active inflammation, such as that related to smoking.

However, whether dietary intake of n-3PUFA is associated with inflammatory reactions in the general population has not yet been fully elucidated with regard to smoking status. In this cross-sectional study, we examined the association between dietary intake of n-3PUFA and serum CRP level, and we compared the CRP levels in groups in the Japanese general population categorized by smoking status.

1. Methods

1.1. Study subjects

The Iwate-KENCO Study (Iwate KENpoku COhort Study) is a prospective cohort study of 26,472 Japanese men and women who are undergoing annual health check-ups [15]. The baseline survey was carried out between 2002 and 2004. Of these participants, 14,191 participants aged 40–69 years with serum CRP levels less than 10 mg/L completed anthropometrical examinations, blood tests, self-administered questionnaires regarding lifestyle, and food frequency questionnaires. All participants provided written informed consent prior to participation in the study. The study was approved by the Medical Ethics Committee of Iwate Medical University and conducted in accordance with the guidelines of the Declaration of Helsinki.

1.2. Measurements

Anthropometrical examinations and blood pressure measurements were performed in a unified manner [15]. Self-administered questionnaires about demographic characteristics, history of cardiovascular disease, drug use, alcohol consumption, and smoking were used to collect individual information. Dietary habits during the previous month were assessed using a brief self-administered diet history questionnaire (BDHQ). This was a 4-page structured questionnaire consisting of three sections: general dietary behavior and major cooking methods, frequency and amount of intake of five alcoholic beverages, and frequency of consumption of 50 selected food and nonalcoholic beverage items. The food and beverage items and the standard portion sizes in the BDHQ were derived primarily from a self-administered diet history questionnaire, a 16-page structured questionnaire consisting of seven sections, which was used previously by one of the authors [18,19]. Estimated dietary intake of 48 food and beverage items, energy, and nutrients were calculated using an ad hoc computer algorithm for the BDHQ, which was based primarily on the Standard Tables of Food Composition in Japan [20]. Pearson's correlation coefficients between intakes assessed using the BDHQ and 16-day semi-weighed dietary records in 92 men and 92 women were 0.24 and 0.26 for energy, 0.34 and 0.33 for cholesterol, 0.50 and 0.55 for fat, 0.55 and 0.60 for saturated fatty acid, 0.50 and 0.57 for monounsaturated fatty acid, and 0.38 and 0.40 for polyunsaturated fatty acid (energy density values), respectively (unpublished observations, Sasaki, 2004). In addition, the intake of eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) assessed using the BDHQ was significantly and positively correlated with serum concentrations of EPA + DHA: Pearson's correlation coefficients were 0.37 ($p < 0.001$) in 91 men and 0.31 ($p < 0.01$) in 91 women (unpublished observations, Sasaki, 2004).

Serum levels of CRP were determined by the latex-enhanced immunonephelometric method (Dade Behring Diagnostics, Germany) using a threshold of 0.1 mg/L. In this estimation, CRP values under the minimum detectable level were treated as 0.1 mg/L. Methods for measuring total cholesterol (TC) levels, triglyceride (TG) levels, high-density lipoprotein cholesterol (HDLC) levels, low-density lipoprotein cholesterol (LDLC) levels, plasma glucose levels, and glycosylated hemoglobin (HbA_{1c}) levels were previously described in detail [15].

1.3. Classification and definition

The male and female subjects were divided into groups according to their smoking status (current smokers, ex-smokers, and nonsmokers). To examine the extent to which dietary intake of n-3PUFA affects serum lipid levels and CRP levels, we divided the male and female subjects into quartile groups according to their dietary intake of n-3PUFA. Several studies have shown that alcohol intake [21] and exercise [22] are associated with serum CRP levels. Regular drinking was defined as drinking 5 days or more per week, and regular exercise was defined as exercising (at least 60 min) 8 days or more per month.

1.4. Statistical analysis

Student's t-test was used to test for differences in several parameters between two groups. A chi square test was used to compare frequencies between categories. Comparisons of skewed data were performed using a Mann–Whitney U test. To determine confounding factors that could affect the association between dietary intake of n-3PUFA and serum CRP levels, sex-specific multiple linear regression analyses were performed using natural logarithm-transformed CRP (ln CRP) as a dependent variable and smoking status patterns (current smoking and past smoking), regular drinking, regular exercise, age, BMI, SBP, intake of saturated fatty acid, intake of n-6PUFA, intake of n-3PUFA, HbA_{1c} level, HDLC level, and LDLC level as independent variables.

After adjusting for factors (those significantly related to ln CRP levels in multiple regression analysis), adjusted CRP levels (expressed as geometric means) of the quartile groups were compared using analysis of covariance (ANCOVA). Adjusted CRP levels were also compared between quartile groups according to intake of long-chain n-3PUFA (EPA + DHA) or according to intake of alpha linolenic acid (ALA). Multiple comparisons were performed using Bonferroni's method. Linear trends across quartile groups were confirmed after adjusting for confounding factors both in male subjects and female subjects. Linear trend tests were also performed across quartile groups separately by smoking status. All p values were based on two-sided tests, and p values less than 0.05 were considered statistically significant. The Statistical Package for Social Sciences (SPSS Japan Inc., Tokyo, version 14.0) was used for all analyses.

2. Results

Table 1 shows the demographic, biochemical, lifestyle, and dietary characteristics of the male and female subjects for all smoking status. The proportions of current smokers were 35.5% in the male subjects and 3% in the female subjects. Crude CRP levels in the male subjects were higher than those in the female subjects (mean values: 0.86 in male subjects and 0.71 mg/L in female subjects, $p < 0.05$). Mean dietary intake of n-3PUFA was 4.0 g/day (1.4% of total energy intake) in the male subjects and 3.3 g/day (1.6% of total energy intake) in the female subjects, intake of saturated fatty acid was 15.5 g/day (5.5% of total energy intake) in the male subjects and 13.8 g/day (6.7% of total energy intake) in the female subjects, and the ratio of n-6PUFA to n-3PUFA in the diet was 3.3 in the male subjects and 3.4 in the female subjects. Mean age was higher in nonsmokers than in others both in male and female subjects. The proportion of regular drinkers was higher than that of ex-drinkers or nondrinkers in current smokers both in men and women.

Table 2 shows the demographic, biochemical, and lifestyle characteristics of the subjects by quartile groups created according to the dietary intake of n-3PUFA. Higher intake of n-3PUFA was associated with more advanced of age, higher SBP, lower TG levels, and lower LDLC levels in the male subjects. In the female subjects, a higher intake of n-3PUFA was associated with more advanced age, lower TG levels, and higher HDLC levels. Crude CRP levels in the lowest

Table 1
Demographic, biochemical, lifestyle, and dietary characteristics of the study subjects

	Male subjects			Female subjects		
	Nonsmoker	Ex-smoker	Current smoker	Nonsmoker	Ex-smoker	Current smoker
Subjects (n)	1547	1261	1543	9399	148	293
Age (years)	60.4 (7.2)	59.9 (7.6)	56.6 (8.3)	57.9 (7.7)	24.0 (3.3)	51.3 (7.4)
BMI (kg/m^2)	24.4 (2.9)	24.5 (2.8)	23.7 (2.9)	24.0 (3.3)	24.4 (4.2)	23.4 (3.9)
SBP (mmHg)	129.5 (18.8)	130.2 (18.7)	127.3 (19.6)	123.5 (19.3)	120.0 (19.4)	118.0 (19.1)
TC (mg/dL)	193.8 (32.6)	197.5 (31.7)	192.1 (33.8)	207.0 (32.2)	202.1 (33.8)	205.0 (35.0)
TG (mg/dL)	122.8 (77.5)	137.9 (100.1)	142.2 (95.2)	111.7 (64.4)	114.1 (70.8)	135.9 (155.2)
HDLC (mg/dL)	56.9 (15.2)	56.4 (15.3)	55.4 (15.2)	61.9 (14.3)	65.0 (15.7)	62.7 (15.2)
LDLC (mg/dL)	115.4 (29.0)	118.0 (28.2)	113.6 (31.9)	124.7 (28.9)	117.8 (29.0)	121.0 (32.2)
PG (mg/dL)	112.9 (31.4)	113.4 (33.3)	113.9 (38.9)	105.2 (24.8)	101.0 (20.2)	101.5 (32.4)
HbA_{1C} (%)	5.08 (0.67)	5.15 (0.76)	5.14 (0.77)	5.08 (0.62)	4.98 (0.59)	5.01 (0.71)
CRP (mg/L)	0.75 (1.14)	0.89 (1.24)	0.95 (1.24)	0.71 (1.08)	0.77 (1.26)	0.74 (1.25)
% of drinkers	42.0%	50.5%	58.6%	4.3%	19.6%	18.8%
% of Reg ex	16.9%	20.6%	11.9%	11.5%	13.5%	15.4%
Ex/month	3.68 (8.56)	4.39 (9.29)	2.63 (7.48)	2.30 (6.74)	2.73 (7.05)	3.53 (8.65)
Dietary intake of each variable: expressed as g/day (% of total energy)						
Carbohydrate	358.8 (56.3%)	337.9 (55.0%)	348.3 (54.8%)	260.1 (57.3%)	238.0 (55.6%)	232.2 (55.4%)
Protein	97.4 (15.3%)	93.5 (15.2%)	92.5 (14.5%)	74.2 (16.1%)	65.5 (15.1%)	65.5 (15.2%)
Total fat	65.0 (22.8%)	61.0 (22.1%)	60.1 (21.1%)	53.4 (25.9%)	50.1 (25.5%)	47.4 (24.8%)
SFA	16.3 (5.8%)	15.5 (5.6%)	14.8 (5.2%)	13.8 (6.7%)	13.5 (6.9%)	12.4 (6.5%)
MUFA	21.8 (7.6%)	20.5 (7.4%)	20.4 (7.1%)	17.9 (8.6%)	17.0 (8.6%)	16.1 (8.4%)
PUFA	17.6 (6.2%)	16.4 (5.9%)	16.4 (5.7%)	14.1 (6.8%)	12.8 (6.5%)	12.3 (6.5%)
n-3PUFA	4.2 (1.5%)	3.9 (1.4%)	3.9 (1.4%)	3.3 (1.6%)	2.8 (1.5%)	2.8 (1.5%)
n-6PUFA	13.2 (4.6%)	12.2 (4.4%)	12.3 (4.3%)	10.6 (5.1%)	10.0 (5.1%)	9.5 (5.0%)
EPA + DHA	2.0 (0.7%)	1.8 (0.7%)	1.9 (0.6%)	1.5 (0.7%)	1.1 (0.6%)	1.2 (0.6%)
α linolenic acid	2.2 (0.8%)	2.1 (0.7%)	2.1 (0.7%)	1.8 (0.9%)	1.7 (0.9%)	1.6 (0.8%)
n6/n3 ratio	3.3 (0.9)	3.3 (1.0)	3.3 (1.0)	3.4 (0.9)	3.6 (0.9)	3.6 (1.0)

Data are expressed as means (S.D.s) or percentages. Abbreviations: BMI, body mass index; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; PG, plasma glucose; HbA1c, percentage of glycosylated hemoglobin; CRP, C reactive protein; smokers, current smokers; drinkers, regular drinkers; Reg ex, regular exercise; SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; n6/n3 ratio, ratio of dietary n-6PUFA to n-3PUFA.

Table 2
Demographic, biochemical, and lifestyle characteristics of the subjects by quartile group (as determined by dietary intake of n-3PUFA)

Q4 groups according to dietary intake of n-3 PUFA (% of total energy)	Q1	Q2	Q3	Q4
	Men (0.15–1.0%) Women (0.24–1.2%)	Men (1.0–1.4%) Women (1.2–1.5%)	Men (1.4–1.7%) Women (1.5–1.9%)	Men (1.7–4.2%) Women (1.9–6.4%)
Male subjects	1088	1087	1088	1088
Age (years)	56.9 (8.6)	58.2 (8.0)	59.5 (7.5)	61.0 (7.0)
BMI (kg/m^2)	24.2 (2.9)	24.1 (2.8)	24.2 (3.0)	24.2 (2.9)
SBP (mmHg)	128.2 (18.9)	129.0 (18.7)	129.1 (19.1)	129.4 (19.8)
TC (mg/dL)	195.7 (33.4)	194.0 (33.4)	195.6 (32.3)	191.8 (32.1)
TG (mg/dL)	144.4 (106)	137.2 (85.6)	134.2 (91.2)	120.7 (78.9)
HDLC (mg/dL)	56.0 (15.2)	55.8 (14.6)	56.9 (15.5)	56.3 (15.6)
LDLC (mg/dL)	116.5 (30.2)	115.7 (30.5)	115.8 (30.0)	113.9 (29.0)
PG (mg/dL)	114.2 (37.8)	111.9 (31.9)	113.0 (31.4)	114.6 (37.4)
HbA$_{1C}$ (%)	5.11 (0.82)	5.10 (0.66)	5.09 (0.63)	5.18 (0.80)
CRP (mg/L)	0.91 (1.25)	0.85 (1.22)	0.84 (1.17)	0.85 (1.19)
Smokers (%)	39.4	37.6	32.8	32.2
Ex-smokers (%)	29.7	28.1	29.4	28.7
Drinkers (%)	54.4	53.4	49.8	43.8
Reg ex (%)	13.2	15.0	18.8	20.6
Female subjects	2459	2460	2460	2461
Age (years)	56.8 (8.1)	56.8 (8.1)	57.7 (7.8)	59.3 (7.1)
BMI (kg/m^2)	24.0 (3.4)	24.0 (3.4)	23.9 (3.3)	24.1 (3.4)
SBP (mmHg)	123.1 (19.3)	123.4 (20.0)	122.6 (18.9)	124.2 (19.1)
TC (mg/dL)	205.6 (32.1)	207.7 (32.5)	206.3 (32.0)	207.9 (32.6)
TG (mg/dL)	116.7 (82.3)	113.5 (65.4)	110.4 (62.3)	109.1 (64.0)
HDLC (mg/dL)	61.4 (14.1)	61.9 (14.5)	62.3 (14.1)	62.4 (14.6)
LDLC (mg/dL)	123.6 (29.2)	125.8 (29.7)	124.1 (28.3)	124.6 (28.8)
PG (mg/dL)	104.8 (26.4)	105.3 (27.3)	104.3 (21.4)	105.7 (24.5)
HBA$_{1C}$ (%)	5.08 (0.67)	5.06 (0.63)	5.06 (0.53)	5.12 (0.65)
CRP (mg/L)	0.74 (1.15)	0.71 (1.10)	0.65 (0.95)	0.75 (1.15)
Smokers (%)	4.1	3.0	2.7	2.1
Ex-smokers (%)	2.0	1.7	1.5	0.9
Drinkers (%)	7.2	4.9	3.9	3.8
Reg ex (%)	9.8	11.0	12.0	13.1

Data are expressed as means (S.D.s) or percentages. Abbreviations are the same as those in Table 1.

Table 3
Standardized regression coefficients by multiple regression analysis predicting logarithm-transformed CRP

	Men (4351)		Women (9840)	
	Standardized coefficient	p value	Standardized coefficient	p value
Age (years)	0.119	<0.001	0.086	<0.001
BMI (kg/m^2)	0.176	<0.001	0.291	<0.001
SBP (mmHg)	0.040	0.008	0.059	<0.001
HDLC (mg/dL)	−0.157	<0.001	−0.131	<0.001
LDLC (mg/dL)	0.057	<0.001	0.043	<0.001
HbA$_{1C}$ (%)	0.084	<0.001	0.091	<0.001
Current smoking	0.149	<0.001	0.013	0.179
Ex-smoking	0.074	<0.001	0.005	0.610
Regular drinking	0.041	0.022	−0.006	0.551
Regular exercise	−0.018	0.216	−0.014	0.138
Carbohydrate intake (%)	−0.017	0.424	−0.037	0.070
SFA intake (%)	0.047	0.014	0.017	0.235
n3 intake (%)	−0.054	0.010	−0.038	0.012
n6 intake (%)	−0.012	0.518	−0.008	0.464

Abbreviations are the same as those in Table 1.

Table 4
Crude means of CRP level and adjusted geometric means of CRP level by groups according to dietary intake of n-3PUFA, by groups according to dietary intake of EPA and DHA or by groups according to dietary intake of α linolenic acid

Dietary intake of n-3 PUFA (% of total energy)	Q1 Men (0.15–1.0%) Women (0.24–1.2%)	Q2 Men (1.0–1.4%) Women (1.2–1.5%)	Q3 Men (1.4–1.7%) Women (1.5–1.9%)	Q4 Men (1.7–4.2%) Women (1.9–6.4%)	Trend *p*
Male participants (*n*)	1088	1089	1089	1088	
CRP (mg/L)	0.91	0.85	0.84	0.85	
Adjusted CRP (mg/L)	0.54 (0.51–0.58)	0.48 (0.46–0.51)	0.48 (0.45–0.51)	0.46 (0.43–0.49)	<0.001
Female participants (*n*)	2461	2461	2461	2461	
CRP (mg/L)	0.74	0.71	0.65	0.75	
Adjusted CRP (mg/L)	0.44 (0.42–0.46)	0.43 (0.41–0.45)	0.41 (0.39–0.43)	0.42 (0.40–0.43)	0.011
Dietary intake of EPA & DHA (% of total energy)	Q1 Men (0.00–0.36%) Women (0.00–0.39%)	Q2 Men (0.36–0.57%) Women (0.39–0.63%)	Q3 Men (0.57–0.85%) Women (0.63–0.91%)	Q4 Men (0.85–3.4%) Women (0.91–4.3%)	Trend *p*
Male participants (*n*)	1088	1089	1089	1088	
CRP (mg/L)	0.89	0.86	0.84	0.85	
Adjusted CRP (mg/L)	0.52 (0.49–0.56)	0.50 (0.47–0.53)	0.48 (0.45–0.51)	0.46 (0.43–0.49)	0.002
Female participants (*n*)	2461	2461	2461	2461	
CRP (mg/L)	0.71	0.70	0.71	0.73	
Adjusted CRP (mg/L)	0.44 (0.42–0.45)	0.43 (0.41–0.44)	0.42 (0.40–0.44)	0.41 (0.40–0.43)	0.044
Dietary intake of α linolenic acid (% of total energy)	Q1 Men (0.13–0.55%) Women (0.18–0.68%)	Q2 Men (0.55–0.72%) Women (0.68–0.85%)	Q3 Men (0.72–0.92%) Women (0.85–1.1%)	Q4 Men (0.92–3.5%) Women (1.1–3.1%)	Trend *p*
Male participants (n)	1088	1089	1089	1088	
CRP (mg/L)	0.93	0.82	0.91	0.80	
Adjusted CRP (mg/L)	0.53 (0.50–0.56)	0.48 (0.46–0.51)	0.49 (0.46–0.52)	0.46 (0.43–0.49)	0.004
Female participants (n)	2461	2461	2461	2461	
CRP (mg/L)	0.76	0.70	0.69	0.70	
Adjusted CRP (mg/L)	0.44 (0.42–0.45)	0.42 (0.41–0.44)	0.42 (0.40–0.43)	0.42 (0.41–0.44)	0.207

Data are expressed as crude means or adjusted geometric means (95% CI). Adjusted geometric means of CRP level for persons aged 60 years with BMI of 24 (kg/m^2), SBP of 128 (mmHg), HDLC of 56.0 (mg/L), LDLC of 117.0 (mg/L) HbA1c of 5.10 (%), intake of saturated fatty acid of 5.5% of total energy, current smoking, ex-smoking, and regular drinking (mean). 95% CI (confidence interval) is based on standard errors from analysis of covariance.

quartile group were higher than those in each of the other three groups for the male subjects ($p < 0.05$, Mann–Whitney U test). On the other hand, there was no difference between mean crude CRP levels in the quartile groups for the female subjects. Higher intake of n-3PUFA was associated with lower percentage of smokers, lower percentage of drinkers, and higher percentage of subjects performing regular exercise.

Table 3 shows the results of multiple linear regression analyses using ln CRP as the dependent variable and smoking status patterns and other factors as independent variables. "Current smoking" and "ex-smoking" were significantly correlated with ln CRP levels in the male subjects but not in the female subjects. Age, BMI, systolic blood pressure, levels of HDLC, LDLC, and HbA1c, intake of SFA, and intake of n-3PUFA were related to ln CRP level in both sexes. Regular drinking was also correlated with ln CRP level, but regular exercise was not associated with ln CRP level. The high levels of correlation among the explanatory variables produce challenges for statistical modelling to ensure the results are not artifacts of collinearity. We also performed multiple regression analyses using the products of pairs of explanatory variables as independent variables to adjust for interactions between explanatory variables. The results were unchanged even after adjusting for interactions between explanatory variables (data not shown).

Non-adjusted and adjusted geometric mean levels of CRP in the quartile groups according to intake of n-3PUFA, according to intake of long-chain n-3PUFA, or according to intake of ALA are shown in Table 4. Multiple comparisons showed significant difference only between the Q1 category and Q4 category according to intake of n-3PUFA (0.54 vs. 0.46, $p < 0.05$) in male subjects. Linear trends across quartile groups according to intake of n-3PUFA or according to intake of long-chain n-3PUFA existed both in male and female subjects. The higher the intake of n-3PUFA was, the lower adjusted CRP level was. The higher the intake of long-chain PUFA was, the lower the adjusted CRP level was. A linear trend across quartile groups according to intake of ALA existed only in male subjects. In female subjects, slightly elevated CRP levels in Q1 and equal levels in Q2, Q3, and Q4 categories were observed.

Table 5 shows adjusted geometric means of CRP level in the quartile groups separately by smoking status. Linear trends across quartile groups were shown in both smokers and ex-smokers in the male subjects. Multiple comparisons showed significant differences in CRP levels between the Q1 and Q2 categories, between the Q1 and Q3 categories, and between the Q1 and Q4 categories in male smokers (0.54 vs. 0.48, 0.48, 0.48, or 0.46, $p < 0.05$). The difference between CRP levels in the Q1 and Q4 categories was also significant in male ex-smokers. A significant difference was not

Table 5
Adjusted geometric means of CRP level in the quartile groups according to dietary intake of n-3PUFA separately by smoking status

Dietary intake of n-3 PUFA (% of total energy)		Q1 Men (0.15-1.0%) Women (0.24-1.2%)	Q2 Men (1.0-1.4%) Women (1.2-1.5%)	Q3 Men (1.4-1.7%) Women (1.5-1.9%)	Q4 Men (1.7-4.2%) Women (1.9-6.4%)	trend *p*
Male nonsmokers	(n)	336	374	411	426	
Adjusted CRP	(mg/L)	0.43 (0.38-0.48)	0.42 (0.38-0.46)	0.42 (0.38-0.46)	0.39 (0.35-0.43)	0.232
Male ex-smokers	(n)	323	306	320	312	
Adjusted CRP	(mg/L)	0.57 (0.51-0.64)	0.48 (0.43-0.54)	0.47 (0.42-0.52)	0.46 (0.41-0.51)	0.009
			$p < 0.05$			
Male smokers	(n)	429	407	357	350	
Adjusted CRP	(mg/L)	0.54 (0.51-0.58)	0.48 (0.46-0.51)	0.48 (0.45-0.51)	0.46 (0.43-0.49)	0.029
		$p < 0.05$				
			$p < 0.05$			
			$p < 0.05$			
Female nonsmokers	(n)	2,310	2,343	2,358	2,388	
Adjusted CRP	(mg/L)	0.44 (0.42-0.46)	0.43 (0.41-0.44)	0.41 (0.39-0.42)	0.41 (0.39-0.43)	0.005
Female ex-smokers	(n)	48	43	36	21	
Adjusted CRP	(mg/L)	0.43 (0.31-0.60)	0.47 (0.32-0.67)	0.52 (0.36-0.77)	0.68 (0.42-1.09)	0.097
Female smokers	(n)	101	74	66	52	
Adjusted CRP	(mg/L)	0.56 (0.44-0.71)	0.48 (0.37-0.63)	0.41 (0.31-0.55)	0.58 (0.43-0.79)	0.605

Data are expressed as adjusted geometric means (95% CI). Adjusted geometric means of CRP level for persons aged 60 years with BMI of 24 (kg/m^2), SBP of 128 (mmHg), HDLC of 56.0 (mg/L), LDLC of 117.0 (mg/L) HbA1c of 5.10 (%), intake of saturated fatty acid of 5.5% of total energy, and regular drinking (mean). 95% CI (confidence interval) is based on standard errors from analysis of covariance. *p* values were determined by analysis of covariance. Multiple comparisons were performed using Bonferroni's method.

found in CRP levels between the groups in male nonsmokers. Although differences in CRP levels between groups were small, a significant linear trend across the quartiles was found in female nonsmokers.

3. Discussion

The main findings of this study were (1) adjusted CRP levels were inversely associated with dietary intake of n-3PUFA or dietary intake of long-chain n-3PUFA for both the male subjects and female subjects, (2) the inverse relationship between adjusted CRP levels and dietary intake of n-3PUFA was more evident in smokers than in nonsmokers in the male subjects, and (3) male smokers taking a low dose of n-3PUFA (in the lowest quartile group) had significantly higher levels of adjusted CRP than those in other male subjects.

Although a linear trend between dietary intake of n-3PUFA and serum CRP levels exists, we also plotted the adjusted geometric mean CRP levels in 20 equally partitioned subgroups according to their intake of n-3PUFA in order to show a non-linear effect between CRP levels and intake of n-3PUFA. An interpolation curve obtained by using spline function showed a steep descent between categories 2 and 3 and a gradual descent between C3 and C20. The spline curve suggests that a cutoff point exists at the C3 point (i.e., 0.91% of energy) and this point possibly means n-3PUFA requirement to maintain attenuated inflammatory reaction (see additional figure as supplementary appendix).

This study also revealed gender-based differences in CRP levels. However, when subjects were limited to nonsmokers, the adjusted CRP levels were almost the same in the male and female subjects (0.42 mg/L in male nonsmokers vs. 0.44 mg/L in female nonsmokers). Considering the low rate of smoking among women and the high rate of smoking among men in this study, the sex-based difference in adjusted CRP levels is probably due to the difference in smoking prevalence between men and women.

The results of this study suggest that activated inflammation is independently attenuated by high-dose dietary intake of n-3PUFA, especially in male smokers. Since n-3PUFAs are precursors of anti-inflammatory eicosanoids (such as prostaglandin I3, prostaglandin E3, thromboxane A3, and leukotriene B5), n-3PUFAs are hypothesized to attenuate the inflammatory response [23,24]. Several studies have been carried out to determine the associations between dietary intake of n-3PUFA (or fish) and levels of inflammatory markers. Pischon et al. showed that dietary intake of n-3PUFA was inversely associated with plasma levels of soluble tumor necrosis factor (TNF) receptors and somewhat less with C-reactive protein in healthy men and women [23,25]. Ciubotaru et al. showed that dietary fish oil reduces levels of C-reactive protein and interleukin-6 in postmenopausal women undergoing hormone replacement therapy (HRT) [26]. These studies suggest that intake of n-3PUFA (or fish) decreases the levels of inflammatory cytokines and CRP levels in healthy subjects. The effect of n-3PUFA intake on serum CRP levels is more evident in high-risk subjects, such as women undergoing HRT. Some studies showed that both CRP levels and other inflammation-related markers were influenced by intake of n-3PUFA. However, we did not measure the levels of interleukins, TNF-alfa, or other inflammation-related agents such as matrix metalloproteinase or macrophage colony-stimulating factor, and we therefore can not discuss the possibility of effects on different inflammation-related pathways due to n-3PUFA.

Rodriguez et al. showed that the favorable effects of fish consumption were more evident in male smokers than that in male nonsmokers in Japanese Americans living in Hawaii [17]. Notably, the apparent preventive effects of fish consumption on cardiac events in their study and the apparent anti-inflammatory effect of dietary intake of n-3PUFA in our study are commonly observed in male smokers. Although the underlying biochemical mechanism was not discussed in their report, the anti-inflammatory effects of n-3PUFA are thought to contribute to the mechanisms that decrease cardiac events in heavy-smoking males.

Several limitations to our study should be noted. The cross-sectional design of the present study tolerates uncertainty of causal relationships. A single instance of blood sampling may be susceptible to short-term variation. Because determination of dietary variables, including fatty acid, was based on a self-administered food frequency questionnaire, information on dietary variables might have been overestimated or underestimated. Socio-economical status (SES) is one of the important confounding factors. However, there was little information about SES in this study and this is one of the limitations. Exercise habit is also one of the important factors that are associated with CRP levels. We performed regression analysis using exercise-related variables and other factors as explanatory variables in three ways: regular exercise, times per month, and quartile categories. There was no relationship between exercise habit and CRP levels in any of the three patterns. We thought that information about exercise in this study was not sufficient for adjusting for confounding effects. The small numbers of female ex-smokers (1.5%) and female nonsmokers (3%) limited statistical power to draw strong conclusions about these groups. The small number of individuals who consumed small amount of n-3PUFA was also one of the limitations.

Despite the lack of causal relationships, based on our findings and those of others, it is reasonable to conclude that sufficient dietary intake of n-3PUFA may attenuate inflammatory reaction and that this effect is more evident in high-risk populations such as male smokers.

Acknowledgements

The Iwate-KENCO study was supported by grants from the Open Translational Research Center Project, Advanced