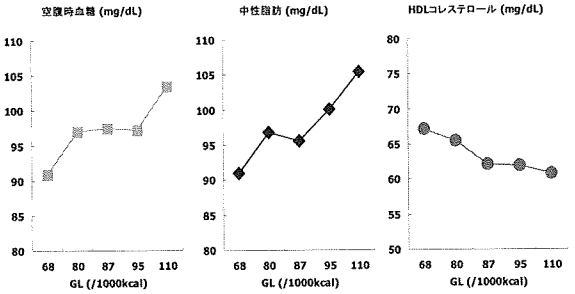
食事のGLが高くなるほど、中性脂肪と空腹時血糖が高くなり、HDLコレステロールが低くなる



全国 5 地域の農村に住む日本人女性 1,345人(20-78歳)。食事 1000 kcal当たりのグリセミックロード(GL)とメタボリックファクターとの関連。GL=GI × 食材中の炭水化物量／100

(Murakami K, 2006)

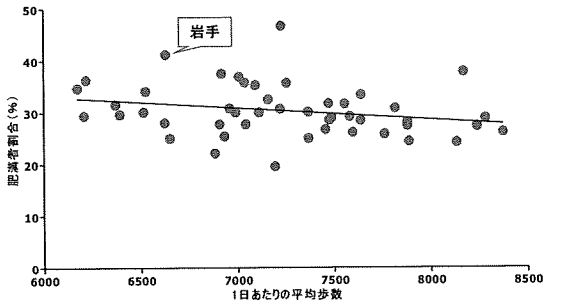
日本人による日本食のグリセミックインデックス 米飯を100とした場合

糖液	122	米飯と味噌汁	74
せんべい	111	米飯と納豆	68
赤飯	105	米飯とヨーグルト	71
もち	101	米飯と牛乳	69
米飯	100	すし飯	67
粥	99	うどん	58
バターライス	96	スパゲッティ	56
白パン	92	そば	56

基準食として炭水化物50gを含む米飯(包装米飯147g)を使用してGIを測定

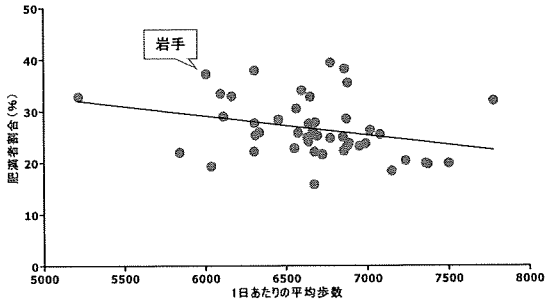
(若木陽子, 杉山みち子らによる)

1日当たりの平均歩数と肥満者割合(男性)



(資料 平成20年度食育白書より作成)

1日当たりの平均歩数と肥満者割合(女性)



(資料 平成20年度食育白書より作成)

日常活動と歩数の換算表

(10分間連続で行った場合)

	日常生活	仕事	歩行	スポーツなど
700歩	洗濯、掃除、炊事、洗面、電車・バスに立って乗る	立って行う軽作業(売り場勤務など)	ぶらぶら歩き(時速 2-3 km)	ドライブ、楽器演奏
1000歩	洗濯物を干す、布団の上げ下ろし、床ふき、窓ふき、入浴・シャワー	軽い肉体労働(園芸)、歩行を主とした軽作業(営業)	普通の速さ(時速 4 km)	ラジオ体操、ゴルフ、ボウリング、ゲートボール
1500歩	芝刈り	中程度の肉体労働(大工、農業)	やや速歩き(時速 5 km)	軽いエアロビクス、社交ダンス
2000歩		強い肉体労働(土木作業、重い物を運ぶ)	速歩き、ジョギング(時速 6 km)	テニス(シングル)、登山

(読売新聞 2008/04/05 健康プラスより)

本日のまとめ

- 岩手県では脳卒中や心臓病の予防が重要
- 岩手県には肥満者が多い
- 血糖がちょっと高め(特に食後)、血圧がちょっと高めは、注意が必要
- 生活習慣の改善、血圧、血糖のコントロールに努めましょう

Ⅳ. 発症登録参加施設名・組織名および研究協力者

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
脳神経外科診療部長	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	東山　　昭
医事課長	阿部　　誠

岩手県立久慈病院

院長	阿部　　正
事務局長	小松　岩松
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	佐藤　敬一
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

九戸地域診療センター

センター長	佐藤　元昭
事務長	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	高橋　正好

済生会岩泉病院

院長	柴野　良博
事務長	藤森　政雄

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	高橋　　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　　柳原　博樹

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
盛岡市、八幡平市、葛巻町、岩手町、滝沢村、雫石町、矢巾町、紫波町

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

研究成果の刊行に関する一覧表

【雑誌(英文)】

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
M Ogawa , F Tanaka, T Onoda , M Ohsawa, K Itai , T Sakai , A Okayama, M Nakamura, On Behalf of the Northern Iwate Heart Disease Registry Consortium	A Community Based Epidemiological and Clinical Study of Hospitalization of Patients With Congestive Heart Failure in Northern Iwate, Japan	Circulation Journal	71	455-59	2007
M Ohsawa , K Itai, T Onoda , K Tanno , S Sasaki , M Nakamura, A Ogawa , K Sakata, K Kawamura ,T Kuribayashi , Y Yoshida , A Okayama	Dietary intake of n-3 polyunsaturated fatty acids is inversely associated with CRP levels, especially among male smokers	Atherosclerosis	201	184-91	2008
S Makita , M Nakamura, K Satoh , F Tanaka, T Onoda , K Kawamura, M Ohsawa, K Tanno, K Itai , K Sakata , A Okayama, Y Terayama , Y Yoshida, A Ogawa	Serum C-reactive protein levels can be used to predict future ischemic stroke and mortality in Japanese men from the general population	Atherosclerosis	204	234-38	2009
T Takahashi , M Nakamura, T Onoda , M Ohsawa, K Tanno , K Itai , K Sakata , M Sakuma, F Tanaka , S Makita, Y Yoshida , A Ogawa, K Kawamura, A Okayama	Predictive value of plasma B-type natriuretic peptide for ischemic stroke: A community-based longitudinal study	Atherosclerosis	207	298-303	2009

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
M Ohsawa , K Itai , K Tanno , T Onoda , A Ogawa, M Nakamura , T Kuribayashi , Y Yoshida, K Kawamura , S Sasaki, K Sakata , A Okayama	Cardiovascular risk factors in the Japanese northeastern rural population	International Journal of Cardiology	137	226-35	2009
M Nakamura ,F Tanaka , T Onoda, T Takahashi , T Segawa , K Kawamura, K Tanno , M Ohsawa , K Itai , K Sakata, S Makita , A Okayama, On behalf of the Iwate KENCO study groups	Gender-specific risk stratification with plasma B-type natriuretic peptide for future onset of congestive heart failure and mortality in the Japanese general population	International Journal of Cardiology	In press	In press	In press
M Sakuma , M Nakamura, F Tanaka , T Onoda, K Itai , K Tanno, M Ohsawa , K Sakata, Y Yoshida, K Kawamura, S Makita, A Okayama	Plasma B-type Natriuretic Peptide Level and Cardiovascular Events in Chronic Kidney Disease in a Community-based Population	Circulation Journal	In press	In press	In press

【雑誌(和文)】

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
横川博英、安村誠司、丹野高三、大澤正樹、小野田敏行、板井一好、川村和子、坂田清美	閉じこもりと要介護発生との関連についての検討	日本老年医学会雑誌	46(5)	447-57	2009

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
栗林徹、大澤正樹、丹野高三、小野田敏行、板井一好	岩手県北部地域住民の肥満に関する考察:岩手県北地域コホート研究の登録時横断解析結果より	岩手公衆衛生学会誌	20(2)	33-45	2009
小野田敏行、丹野高三、大澤正樹、板井一好、坂田清美、小川 彰 、小笠原邦昭、田中文隆、中村元行、大間々真一、吉田雄樹、石橋靖宏、寺山靖夫、栗林 徹、川村和子、松舘宏樹、岡山 明	岩手県北地域における死亡、脳卒中と心筋梗塞罹患、心不全発症および要介護認定状況について～岩手県北地域コホート研究の平均2.7年の追跡結果から～	日本循環器予防学会誌	45(1)	32-48	2010
丹野高三、栗林 徹、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、吉田雄樹、小川 彰、寺山靖夫、川村和子、岡山 明	高齢者の body mass index と総死亡、循環器疾患罹患との関連～岩手県北地域コホート研究の2.7年の追跡調査より～	日本循環器予防学会誌	45(1)	9-21	2010

Ⅵ. 研究成果の刊行物・別冊

Circ J 2007; **71:** 455–459

A Community Based Epidemiological and Clinical Study of Hospitalization of Patients With Congestive Heart Failure in Northern Iwate, Japan

Muneyoshi Ogawa, MD; Fumitaka Tanaka, MD; Toshiyuki Onoda, MD*; Masaki Ohsawa, MD*; Kazuyoshi Itai, PhD*; Toshiaki Sakai, MD**; Akira Okayama, MD***; Motoyuki Nakamura, MD On Behalf of the Northern Iwate Heart Disease Registry Consortium

Background Community based studies of congestive heart failure (HF) are lacking in the Japanese population.
Methods and Results To delineate the epidemiological and clinical features of advanced HF in the general Japanese population, hospitalized adult cases of HF in all hospitals within the Ninohe district were registered for 3 years. During the survey period, 190 new onset cases (males n=93; females n=97) and a total of 391 hospitalizations (including repeat admissions) were registered. The prevalence of atrial fibrillation in new HF cases was 56% in males and 45% in females. On the basis of the population of the district, the incidence of hospitalized HF was 96 in males and 92 in females per 100,000 person-years. The percentage of HF patients who were ≥65 years of age was 82% in males and 94% in females. In cases undergoing echocardiography, preserved left ventricular systolic function (left ventricular ejection fraction ≥50%) was observed in 29% of males and 41% of females. There was a significant seasonal variation in HF admissions (Spring 32%; Summer 20%; Autumn 20%; Winter 28%; $p<0.01$).
Conclusions In comparison with published results of USA and European community based studies of HF, the present HF cohort showed that: (1) mean age, prevalence of preserved ejection fraction, and trends in seasonal variation were comparable; however (2) the incidence of HF was obviously lower. These epidemiological and clinical characteristics should be taken into consideration when establishing a therapeutic and preventive approach for HF. (*Circ J* 2007; **71:** 455–459)

Key Words: Community; Epidemiology; Heart failure; Incidence; Population; Prevalence

Congestive heart failure (HF) is one of the most common reasons for hospital admission among the elderly in US and European populations[1,2] This increase in prevalence might be caused by rising mean age and improved survival of patients with cardiovascular disease because of therapeutic advances[3,4] Moreover, patients with HF are at high risk of readmission to hospital. In fact, surveys in the USA and Europe have reported that 16–50% of elderly HF patients are readmitted within 6 months of their first admission[2,5–7] As a consequence, HF has become an important public health problem, with increasing prevalence placing a growing burden on health-care systems in these countries[8]

The mean age of the Japanese population is increasing steeply and it is estimated that by the year 2020 25% of the population will be ≥65 years of age. As observed in the USA and Europe, the HF epidemic might become evident in our population. However, there has been a deficiency of population or community based epidemiological studies in the Japanese population to date, leaving a gap in epidemiological data such as incidence, prevalence and prognosis of HF in this country. These data are not simply a matter of curiosity but will be essential for physicians, policy makers, economists, health-care administrators, and pharmaceutical manufacturers.

Although several epidemiological and clinical studies of HF in teaching hospitals have been published or are ongoing in this country[9] no adequate community based data have been reported. We have therefore collected prospective data on all registered hospitalized adult patients with HF over a 3-year period in the Ninohe district, a rural community in northern Iwate where medical facilities are limited and the population is relatively stable. On the basis of this registration survey, we have calculated hospitalization and readmission rates, seasonal variations, and the incidence of preserved left ventricular systolic function and atrial fibrillation in HF patients.

Methods

Study Population

The Ninohe district is a rural area situated in the Iwate prefecture, northeast of Honsyu, Japan (Fig 1). The Ninohe district comprises the city of Ninohe, the towns of Ichinohe, Karumai and Jouboji, and the village of Kunohe. According to annual statistical data for 2003 issued by the Iwate prefecture government, this region had a resident population of 67,307 (32,257 males; 35,050 females). The percentage of the population aged ≥65 years was 26%. Following an in-

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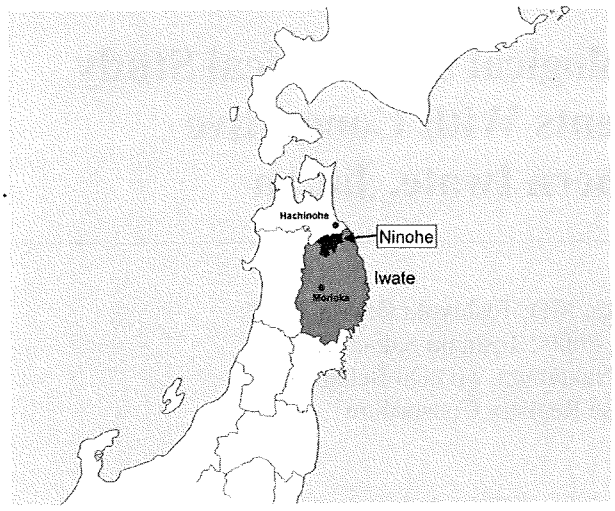

Fig 1. Study area. Ninohe district of Iwate, northern Honsyu, Japan.

tensive briefing on the rationale for the study and discussion of ethical issues, physicians representing all primary care and referral centers in the Ninohe district community agreed to participate. The district contains only 4 public hospitals (Ninohe, Ichinohe, Karumai and Ibonai Hospitals) and 7 private clinics with admission facilities. In addition, to ensure almost complete capture of all HF hospitalizations within the Ninohe district during the study period, registration was extended to include medical centers located in Morioka city (60 km south of Ninohe) including our University hospital and 3 referral medical centers located in Hachinohe city (50 km north of Ninohe). Approval was obtained from the ethics review board of each participating hospital prior to commencement of the study. Because the study protocol involved a review of charts obtained as part of routine medical care only, patient consent was not required.

Inclusion Criteria and Enrolment

Inclusion criteria were based on the Framingham definition of HF;[10] with subjects assigned a diagnosis of HF if either 2 major criteria or 1 major and 2 minor criteria were present concurrently. The major criteria were: paroxysmal nocturnal dyspnea, orthopnea, abnormal jugular venous distention, rales, cardiomegaly, pulmonary edema, presence of a third heart sound, elevated central venous pressure, and weight loss of 4.5 kg or more in 5 days. The minor criteria included: edema, night cough, dyspnea on exertion, hepatomegaly, pleural effusion, tachycardia, and weight loss of 4.5 kg or more in 5 days.

Subjects were enrolled only if they had been hospitalized and fulfilled the following conditions: (1) were established residents of the Ninohe district; (2) were aged ≥20 years; and (3) were admitted between 1 April 2002 and 31 March 2005. Registration was initially performed by attending physicians at each hospital. Patients compatible with the diagnosis of HF in terms of symptoms, physical examination, chest X-rays, and response to treatment were checked by using a registration card after admission. Patients were excluded if they had been hospitalized: (1) to undergo invasive cardiac examination such as cardiac catheterization; (2) for the introduction of β-blocker therapy; (3) with an advanced stage malignant tumor and/or preceding apparent pneumonia; (4) within 4 weeks after onset of acute myocardial infarction; or (5) with end-stage renal failure and without apparent cardiac dysfunction.

Table 1 Comparison of Clinical Characteristics of Patients With Heart Failure Divided by Sex

	Male	*Female*	*All*
No. (n)			
New onset	*93*	*97*	*190*
Readmission	*99*	*102*	*201*
Total	*192*	*199*	*391*
Mean age (years)			
New onset	*73.2±12.7*	*80.1±11.4*	*76.3±13.3*
Readmission	*78.6±10.4*	*82.0±9.7*	*79.9±10.7*
Total	*75.3±12.2*	*81.0±10.7*	*78.1±12.3*
% of age ≥65 years			
New onset	*74*	*92*	*83*
Readmission	*90*	*95*	*92*
Total	*82*	*94*	*88*
% of age ≥80 years			
New onset	*32*	*63*	*48*
Readmission	*56*	*65*	*60*
Total	*42*	*64*	*53*
% of atrial fibrillation			
New onset	*56*	*45*	*50*
Readmission	*44*	*37*	*40*
Total	*53*	*44*	*48*
% of ejection fraction ≥50%			
New onset	*26*	*40*	*33*
Readmission	*33*	*46*	*32*
Total	*29*	*41*	*34*

To ensure that nearly all appropriate cases had been identified, we periodically retrieved and reviewed medical charts and/or discharge summaries for nearly all patients (>99%) admitted to the cardiology and internal medicine wards of all hospitals within the study district. This was carried out by 2 or more members of the study steering committee, which comprised 3 cardiologists, 3 trained research nurses, and 2 epidemiologists. Patients who had been transferred to another hospital were counted on the index admission only. Echocardiographic evaluation such as left ventricular ejection fraction assessment (Simpson or Teichholtz method) was performed for all patients with HF at 1 hospital (Ninohe Hospital) by full-time attending cardiologists, whereas in the remaining hospitals, evaluation was performed by part-time cardiologists in a small percentage of patients only. The percentage of patients who underwent echocardiographic examination was 65%.

Data Analysis

Continuous variables are expressed as mean ± SD. Group comparisons were based on the Student's t-test or chi-square test, as appropriate. Incidence rates were calculated as the observed number of new cases of HF divided by the age- and sex-specific person-years of observation. An estimation of residents in the Ninohe district aged ≥20 years was derived from published census data at October 2003. In addition, the incidence rate was adjusted by using the standard Japanese population. Seasons were defined as follows: Spring=20 March to 19 June; Summer=20 June to 21 September; Autumn=20 September to 20 December; Winter=21 December to 19 March. The significance of seasonal variation was tested by the Roger's method.[11]

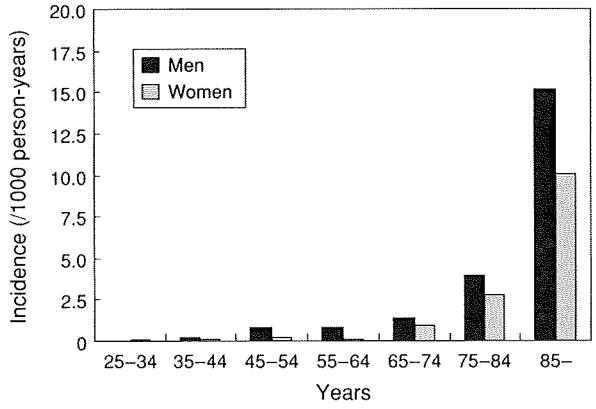

Fig 2. Incidence of heart failure according to the sex and 10-year age group.

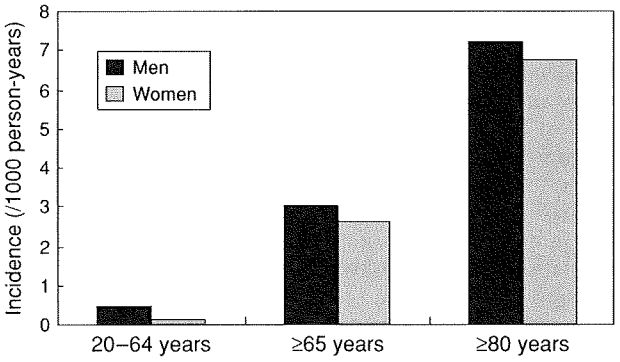

Fig 3. Incidence of heart failure according to sex and age below 65 years, ≥65 years, and ≥80 years.

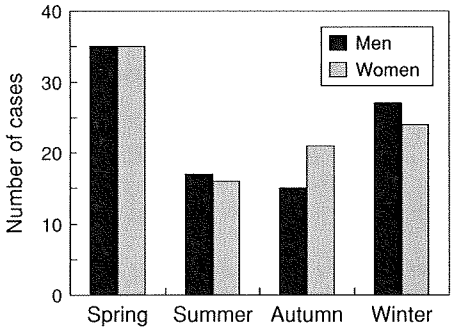

Fig 4. Seasonal variation in the accumulated number of hospitalizations for heart failure during the 3-year study period.

Results

Registered Number of Patients

During the 3-year study period, the total number of HF patients including readmission cases was 391 (192 males; 199 females). This total included 190 cases of new onset (93 males; 97 females), yielding a readmission case of 51% in both sexes. There were no significant differences in the number of registered cases by year (2002, n=118; 2003, n=149; 2004, n=124: NS).

Patient Characteristics

The age range for new onset cases was 35–96 years in males and 28–98 years in females. As shown in Table 1, the mean age was significantly higher in females (81.0± 10.7 years vs males 75.3±12.2 years: $p<0.001$). Within the new onset cohort, 83% were ≥65 years of age (74% males; 92% females: $p<0.01$), and 48% were ≥80 years of age (32% males; 63% females: $p<0.01$).

Atrial Fibrillation

Atrial fibrillation was observed in approximately half of new onset cases (Table 1), with no significant difference between the sexes (56% males; 45% females: NS). Readmission cases showed a comparable trend (44% males; 37% females: NS).

Preserved Ejection Fraction

After exclusion of patients with significant valvular abnormalities, the percentage with a preserved left ventricular ejection fraction of ≥50% was higher in females than in males (41 vs 29%). Thirty-four percent of registered cases were therefore classified as having HF with preserved ejection fraction. Among the new onset HF cases, the ejection fraction was preserved in 40% of females and 26% of males. A similar trend was observed in readmission cases (46% females, 33% males). The mean age of patients who underwent echocardiography was significantly younger than that of patients who did not (76.3±12.5 vs 81.7±10.0 years of age; $p<0.01$).

Incidence

During the 3-year study period, 190 new cases of HF (93 male, 97 female) were diagnosed in the Ninohe district. The crude overall incidence rate was 94 per 100,000 person-years. Male subjects had a slightly higher crude incidence rate at 96 compared to female subjects at 92 per 100,000 person-years. The age- and sex-adjusted incidence rate for the standard Japanese population was 39 per 100,000 person-years. Analysis of incidence rates by age and sex showed a general age-associated increase with male predominance (Fig 2). The incidence rate varied from less than 0.5 per 1,000 person-years in females aged under 65 years to 15 per 1,000 person-years in males aged ≥85 years. As shown in Fig 3, the incidence rates for elderly subjects (≥65 years old) were 3.05 per 1,000 person-years for males and 2.65 per 1,000 person-years for females. In the very elderly (≥80 years), rates were higher at 7.24 per 1,000 person-years for males and 6.76 per 1,000 person-years for females.

Seasonal Variation

The cumulative number of new hospitalized cases during the 3-year study period is shown in Fig 4. There was significant variation by season (Spring 37%; Summer 17%; Autumn 19%; Winter 27%; $p<0.01$). Hospitalization rates in Spring and Winter were greater than 50% higher than in Summer and Autumn. This seasonal variation remained evident when the analysis was performed on all admission cases (including readmissions) (Spring 32%; Summer 20%; Autumn 20%; Winter 28%; $p<0.01$).

Discussion

The present study was conducted in a rural Japanese community where the proportion of the population aged ≥65 years is similar to that predicted for the future Japanese population. We have demonstrated the following new observations: (1) a significant proportion of HF patients

were elderly (aged ≥65 years); (2) approximately half of HF cases showed atrial fibrillation at admission; (3) the prevalence of preserved ejection fraction was significantly higher in females than in males; (4) the incidence of HF was less than 100 per 100,000 person-years; and (5) there was seasonal variation with the onset of HF.

The median age of HF cases as a whole was just under 80 years, with a significantly higher mean age in females than in males. This is comparable to reports in other racial populations.[12–14] Approximately half of the HF patients captured by the present study showed atrial fibrillation at admission. No previous community based study in Japan has reported the prevalence of atrial fibrillation in patients with HF. However, a similar rate has been reported in hospital-based studies.[15,16] There is also evidence of racial variation in the prevalence of atrial fibrillation among patients with HF. Ruo et al have demonstrated that African-Americans had a 50% lower incidence of atrial fibrillation than Caucasians.[17] As incidence rates of atrial fibrillation among Caucasian HF patients have been reported to range from 28 to 42%,[18,19] the prevalence of atrial fibrillation in our patients with HF was somewhat higher than that in other racial populations. However, as atrial fibrillation was prevalent in males and the elderly,[20] sex- and age-adjusted analysis would be essential to determine the racial difference.

Of patients with HF who underwent echocardiography, half of the female cohort showed preserved ejection fraction while only a quarter of males did so. Although there are no previous reports of the incidence of preserved ejection fraction among HF patients in community based Japanese populations, the present value is comparable to that reported from other ethnic populations using the same partition value for left ventricular ejection fraction.[21,22] However, of the potentially eligible patients in the present study, only 65 percent had a documented assessment of left ventricular ejection fraction. This might have resulted in a selection bias. The mean age of patients not undergoing echocardiography was higher than those who did undergo echo examination. As the incidence of preserved ejection fraction is greater in the elderly, this might have been underestimated in the present study.

The incidence of HF in our study community was less than 100 per 100,000 person-years for patients aged 20–65 years. The value rose to approximately 300 per 100,000 person-years in those aged ≥65 years, and approximately 700 per 100,000 person-year in those aged ≥80 years. However, these values are clearly lower than that of published data from the USA and European countries using the same definition of HF.[23–26] The reasons for the low incidence of HF in our population remain unknown on the basis of the present study. However, as the main etiology of HF was recognized as coronary artery disease, 1 reason might be the low prevalence of coronary artery disease in the Japanese population.[27–29] Alternatively, health-care systems differ between countries. Specifically, Japan has a universal health insurance system and most Japanese could visit medical facilities at relatively low cost. In contrast, in the USA, 15% of persons aged under 65 years are uninsured.[30] One may argue, however, that the system for capturing HF cases in the present study might have been incomplete, resulting in the underestimation of incidence. However, we did attempt to retrieve and review all medical charts or discharge summaries from cardiology and internal medicine wards of all hospitals located within the survey district. Moreover, to further reduce the potential for missing cases, the study included several remote teaching hospitals and tertiary referral medical centers located within 100 km of the survey area. This makes it unlikely that a significant number of HF cases would have been lost to the present registry.

Our community based study revealed significant seasonal variation in the onset of new HF as well as acute worsening of the condition. The peak in variation was seen in Winter-Spring compared to Summer-Autumn. A similar seasonal variation has been reported from European countries.[31–33] Although the precise reasons for this variation remain unknown, a potential explanation might be the presence of some other condition with a well-known seasonal variation such as respiratory tract infection, myocardial infarction and ischemia, or high blood pressure. Heart rate and systemic blood pressure have been reported to rise in cold environments, thus increasing cardiac oxygen consumption and cardiac afterload. This, in turn, might increase the onset of HF during the Winter-Spring season in a cold climate.

Despite the advantages afforded by our community based study, several limitations must be considered when the results are interpreted. First, registration was restricted to hospitalized patients so that HF patients treated at an outpatient clinic only might be missing from the registry, resulting in an underestimation of the incidence of HF. However, physicians are less likely to treat a severe HF patient without hospitalization as the Framingham criteria used in this study tended to capture relatively advanced HF. Second, this community based study was limited to the Ninohe district, a rural area in Northeast Japan, and might therefore be restricted in its generalizability to other areas in Japan. However, other ethnicities are very rare in the Japanese population (less than 2%), making the genetic background relatively homogeneous. Moreover, the percentage of the population aged ≥65 years in the survey area is identical to the value predicted for the Japanese population in 2020. In light of this, the present study results might assist our understanding of the future epidemiological setting of HF in this country. Third, as the determination of exact etiology of HF (ie, coronary artery disease, hypertensive heart disease, valvular heart disease, cardiomyopathy, myocarditis) by non-invasive examination in an epidemiological setting has been reported to be difficult,[34] we did not attempt to classify the etiology of HF in this study. Specifically, a predominantly elderly population is unlikely to be systematically examined in detail for possible coronary artery disease by coronary angiography or stress myocardial perfusion imaging. Finally, the present study did not evaluate the prognosis of HF, and thus could not compare the prognosis for Japanese patients with HF to that of other racial populations. Further community based studies using a follow-up design would be needed to answer this question.

In conclusion, when compared with USA and European community based studies of HF, the present HF cohort has shown that: (1) mean age, prevalence of preserved ejection fraction, and seasonal variability were comparable; however, (2) the incidence rate was obviously lower. These epidemiological and clinical characteristics should be taken into consideration when establishing therapeutic and preventive strategies for HF.

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

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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

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[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.