原　著

岩手県透析患者の悉皆的コホート研究：2年間の追跡調査結果報告

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要　約　カレン研究は岩手県北部地域を対象とした成人透析患者の悉皆性コホート研究で、2003年6月から2004年3月までに登録調査を終えた。参加同意者の内1,214名(全体の81%)で血液検査を含めた登録調査を実施した。25透析施設を直接訪問して、1,214名の透析患者診療記録を1年ごとに閲覧した。平成19年4月の時点で、転院先での詳細な追跡調査が終了していないものが69名存在している。生存分析による解析は1,145名を対象に検討した。総観察人年は2,215人年であった。観察期間中に189名の死亡、214名の心不全発症、29名の急性心筋梗塞発症、107名の脳血管疾患発症を確認した。死亡率は85/1000人年で、死亡率に性差はなく、原疾患別で比較すると糖尿病性腎症患者の死亡率が高かった($p < 0.01$)。Cox回帰分析による検討では、死亡に影響していたリスク要因として、年齢(ハザード比(95%信頼区間)：1.047(1.033-1.062))、糖尿病合併(1.502(1.096-2.058))、C型肝炎抗体陽性(1.546(1.015-2.356))、血清低アルブミン値(2.272(1.657-3.117))、血清高CRP値(1.907(1.403-2.591))、があげられ、これらの要因は、循環器疾患合併、悪性新生物合併の有無に関わらず、死亡の強いリスク要因であった。

キーワード：透析患者，死亡率，危険因子，心血管疾患，悉皆性コホート研究，カレン研究
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I. 緒　　言

日本の透析患者数は年々増加し、2006年の日本の透析患者総数は約26万人で、100万人あたりに換算すると2,070人と見込まれ、世界で最も多い[1),2)]。透析患者の増加は日本社会にとって、医療経済的にも大きな負担となっており、その対策は急務であり、透析患者の置かれている実態を解明し、具体的な対策を講じることが望まれる。

1990年代に井関らは、沖縄県で透析患者の地域悉皆性コホート研究を立ち上げ、日本人透析患者の実態を明らかにした[3-15)]。井関らの研究から10年が経過し、この間にわが国の透析患者の実態も大きく様変わりした。透析患者の透析導入原因疾患の1位は慢性糸球体腎炎から糖尿病性腎症へと変化し、透析患者の透析導入時年齢は年々高齢化し、透析患者に占める高齢者の割合も増加している。糖尿病患者と高齢の透析患者の増加が透析患者の死亡率を上げる要因となっており、透析技術の進歩にも関わらずわが国の透析患者の死亡率は近年9%前後で横ばいとなっている[1),16)]。

日本透析医学会では、全国の透析施設に郵便により透析患者情報収集を行い、現在の日本人透析

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患者の実態を毎年ウェブ上で公開している[1]。しかし、郵便による情報収集は精度管理に問題があること、集められる情報内容も概要に限られること、縦断研究ではないため患者の罹患率や死亡率を算出することが不可能であるといった点が、疫学情報としては不十分な点である。精度の高い登録調査を行い、かつ死因同定や疾患発症登録に関しての統一規準を設けた追跡調査で、地域ベースで多数の透析患者を対象とした研究が強く望まれる。

高度な精度管理下の研究で、透析患者の疾患罹患率、死亡率、死因を明らかにするとともに、死亡や発症に関わるリスク要因を明らかにすることを目的として、我々は平成15年度に岩手県中央部から北部地域にかけての全ての透析施設を対象として透析患者のコホート研究を開始した[17]。平成20年度までの最低5年間の追跡調査を実施する予定である。本論文では、平成16年度、平成17年度の追跡調査データを基に成人血液透析患者の2年間の生命予後について検討したので報告する。

II. 方　　法

研究対象地域

カレン研究（末期腎不全患者に対する多面的な取り組みにより循環器疾患発症リスクを割り出す研究：Kaleidoscopic Approaches to patients with end-stage RENnal disease, KAREN研究）の対象地域は岩手県北部から県中央部で、平成14年当時の域内には38市町村が含まれ、総人口は939,448人である。カレン研究では、20歳以上の成人透析患者を研究対象とした。透析施設は全部で26施設あり、成人透析患者総数は1,506名であった。人口100万人あたりでは透析患者は1,596人であった（図1-1）。登録調査は2003年6月に始まり、2004年3月まで行った。本研究は岩手医科大学倫理審査委員会の承認を得て、ヘルシンキガイドラインに従って実施された[17]。

研究参加者

研究参加者の内訳を図1-2に示す。25施設1,499名の透析患者の内、全身状態不良者または脳血管性認知症などにより意思疎通が困難だった27名は面会できなかった。残りの1,447名に面会し、1,260名から書面による同意（登録時調査ならびに1年毎の追跡調査に対する）を得た（同意受容率87.0%）。同意が得られた1,260名中21名は病状の悪化や転院により登録調査ができなかった。25名の患者では血液検査がなされなかった。1年ごとに25透析施設を直接訪問して、1,214名の透析患者診療記録を閲覧した。平成19年4月の時点で、転院先での追跡調査が終了していないものが69名存在している。本論文では、2年分の追跡調査が終了した1,145名を解析対象として検討した。

登録調査

登録調査は、調査員の面談による生活問診、血圧測定、身長測定、患者医療記録による患者医療情報収集、透析施行直前の採血による血液検査からなる。登録時調査の詳細については、すでに公表している論文を参照されたい[17]。

追跡調査

直接透析施設を訪問して、患者診療記録ならびに死亡診断書を閲覧して、死亡と死亡原因、循環器疾患発症（冠動脈疾患、心不全、脳血管疾患）の有無、悪性新生物発症の有無について追跡調査を行った。カレン研究開始時に研究チームで協議して一定の基準を設けた[17]。疾患定義は表1に示したとおりである。尚、脳卒中の診断基準において、脳出血、脳梗塞、くも膜下出血の診断は、画像診断で確認した

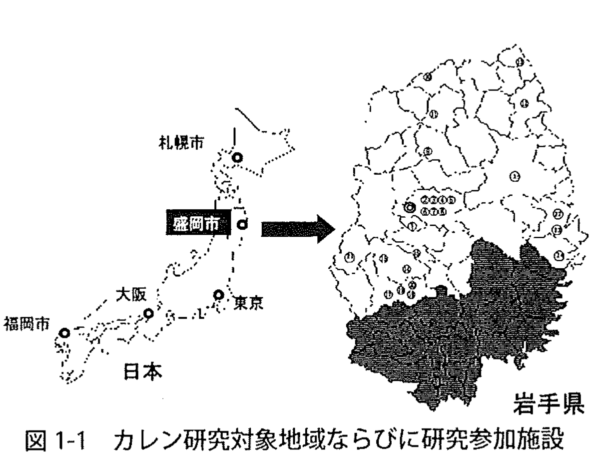

図1-1　カレン研究対象地域ならびに研究参加施設

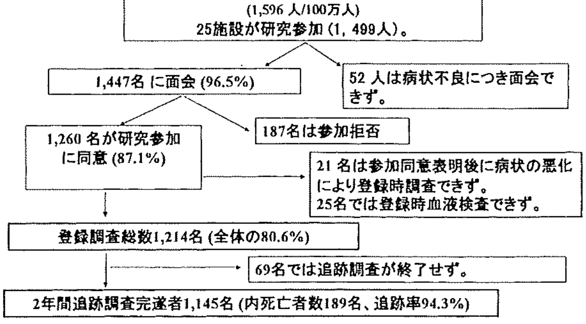

図1-2　研究参加者のフローチャート

表1　KAREN研究腎不全原因疾患診断ならびに合併疾患、新規発症疾患診断基準

腎不全原因疾患診断基準

慢性糸球体腎炎

1 血尿
2 蛋白尿(2+、3+)
3 長期にわたる腎機能低下

上記臨床症状1～3を満たすもの、または腎生検診断されたものを慢性糸球体腎炎と定義する。

糖尿病性腎症

1 糖尿病と診断されている
2 蛋白尿(300mg/日以上)・浮腫・高血圧・腎機能低下(一つ以上)

上記の1と2を満たすもの、あるいは腎生検診断されたものを糖尿病性腎症と定義する。

腎硬化症

1 蛋白尿(±、+)
2 高血圧
3 長期にわたる腎機能低下

上記1～3を満たすもの、または腎生検診断されたものを腎硬化症と定義する。

多発性嚢胞腎

腹部US・CTにて両側に多発性嚢胞を認めるものを多発性嚢胞腎と定義する。

膠原病に起因する腎炎

膠原病と診断された上で腎機能低下を認め、かつ腎生検診断されたものと定義する。

その他

上記以外の原疾患(薬剤性腎炎、先天性、感染性等)

合併疾患、新規発症疾患診断基準

心不全

1 肺水腫または胸水貯留(心機能障害の有無、uremic lungかどうかは問わず)を持って所見ありとする。
2 その他の心不全徴候に関しては、心不全に影響を及ぼす左室機能障害または弁膜症の存在の確認を必要とする。
心エコー図による左室駆出率50%未満、大動脈弁または僧帽弁の狭窄または逆流が中等度以上をもって心機能異常ありとする。

心筋梗塞症

1 心電図で最低二つの誘導で異常Q波の出現
2 心筋逸脱酵素の2倍以上の上昇
3 30分以上持続する胸痛

上記の1～3のうちいずれか2項目を含むもので、循環器専門医師の診断をうけているものを心筋梗塞の既往ありとする。

脳卒中

1 突然生じた神経症状(巣症状)が医師により確認され、24時間以上持続
2 神経症状が脳血管疾患以外の病気であることが否定されている
3 CTまたはMRIによる脳梗塞巣または脳出血巣の確認

上記の1、2の両者を同時にみたすもの、または3があるものを脳卒中と診断する。

閉塞性動脈硬化症

1 血管バイパス手術、血管形成術の存在
2 Ankle-arm systolic ratio ≦ 0.8
3 間歇性跛行・大腿部痛

上記の1～3のうちいずれか1項目を含むものを閉塞性動脈硬化症と診断する。

糖尿病

1 糖尿病治療中である
2 随時血糖　≧　200mg/dl
3 HbA1c　≧　6.5%以上

上記の1～3のうちいずれか1項目を含むものを糖尿病と診断する。

高血圧

1 高血圧治療中である
2 収縮期血圧　≧140mmHg以上
3 拡張期血圧　≧　90mmHg以上

上記の1～3のうちいずれか1項目を含むものを高血圧と診断する。

脂質異常

1 高脂血症治療中である
2 高コレステロール血症　≧220mg/dl
3 高LDL-コレステロール血症　≧140mg/dl
4 低HDL-コレステロール血症　<40mg/dl

上記の1～4のうちいずれか1項目を含むものを脂質異常と診断する。

ものとした。転院した症例に関しては、転院先を訪問し、患者診療記録を閲覧して情報収集した。

統計ならびに解析手法

慢性糸球体腎炎患者と糖尿病性腎症患者の割合が大きく、3番目に多い高血圧性腎硬化症患者は10%以下であることから、本論文では慢性糸球体腎炎患者と糖尿病性腎症患者以外をその他の疾患としてまとめて解析した。登録時患者属性比較では、連続変数の比較にはt検定を用い、割合の比較ではχ二乗検定を用いた。3群間の比較には分散分析を用い、多重比較にはBonferroniの修正式を用いた。観察期間は、イベント存在例では登録調査日からイベント発症（死亡、循環器疾患発症）までの年数（人年）を求め、イベントの無いものでは登録調査日から最終調査日時までの期間を観察期間（人年）とした。

性別、原疾患別に死亡数ならびに循環器疾患発症数を求め、1000人年あたりの粗死亡率と循環器疾患罹患率を算出した。性別・原疾患別の死亡率の比較には、カプランマイヤーの生存分析を用いて、ログランク法による有意差検定を行った。

Cox比例ハザードモデルを用いて各危険因子の総死亡のハザード比と95%信頼区間を算出した。古典的循環器疾患危険因子を調整する目的で、年齢とbody mass index (BMI)を説明変数に用いた。尚、BMIの算出にあたり、体重はdry weightを用いた。収縮期血圧の4分位で対象者を分け、最低位カテゴリを血圧低値者群、最高位カテゴリを血圧高値者群と定義して、血圧低値と血圧高値をそれぞれ説明変数とした。脂質異常は、血清総コレステロール値が220 mg/dL以上、またはHDLコレステロール値が40 mg/dL未満、または抗高脂血症薬服用者と定義した。空腹時採血ではなかったため、中性脂肪値は定義基準に取り上げなかった。現在喫煙者を喫煙ありとして説明変数に用いた。週5日以上飲酒している者を常用飲酒者と定義した。血清アルブミンは4分位の最低位グループをアルブミン低値群と定義、血清CRP値は4分位の最高位グループを高CRP値群と定義して、説明変数としてそれぞれ多変量調整分析に用いた。また、合併疾患（心筋梗塞、脳卒中、悪性新生物、糖尿病）の有無も説明変数としてハザード比を求めた。次いで、循環器疾患（心筋梗塞症、脳卒中）または悪性新生物疾患合併患者270名を除いて、上記説明変数を調整してハザード比を求めた。解析では、強制投入法を用いて、有意性の有無に関わらず、全ての項目のハザード比を提示した。P値は両側で5%未満を有意とした。統計解析にはSPSS. Version 14を用いた。

III. 結　果

表2は登録時の患者属性である。患者総数1,214名の平均年齢は61.2歳で最年少は22歳、最年長は95歳であった。男女で年齢の差はみられなかった。透析導入後の平均期間は7.0年であった。透析導入の原因腎疾患の割合をみると、慢性糸球体腎炎が29.8%、糖尿病性腎症が24.5%、腎硬化症が9.8%、多発性嚢胞腎が3.5%、病因不明が24.9%であった。日本透析医学会の報告と比較して原因不明が約25%と非常に多くなっていた。日本透析医学会報告では、腎不全原因疾患の診断は、臨床資料をもとに、限られた研究者が統一基準を基に診断するのではなく、各透析施設に診断が委ねられている。一方、当研究では、表1に示すように厳格に診断基準を設定し、診断基準に合致しないものは、原因不明と分類したことから腎不全原因不明が多くなったことが考えられる。また、病理診断が全体の11%でしか行われていないことも、腎不全原因不明が多かった理由に上げられる。

合併疾患の割合は、心筋梗塞が5.2%、脳卒中が13.1%、閉塞性動脈硬化症が16.1%、高血圧症が87.1%、脂質異常が45.6%であった。糖尿病は男性で32.1%、女性で23.7%であった。尚、透析患者の嗜好習慣をみると、男性ではおよそ4割が現在喫煙者で、一般地域住民と比べても決して低くはない。禁煙者が35.7%もいることから、透析患者に対する禁煙指導は行われているものと思われるが、禁煙対策は十分とはいえないと考えられる。一方男性の常用飲酒者は9%で、男性の禁酒者は44%にも達していたことから、透析患者に対しての禁酒指導は厳しく行われていることが推測される。

表3は腎不全原疾患別に患者属性を比較したものである。平均年齢を見ると、慢性糸球体腎炎患者は、糖尿病性腎症患者やその他の腎不全患者より5歳若かった。平均の透析導入後の期間をみると、糖尿病性腎症患者が3.7年と短かった。また糖尿病性腎症患者は、男性患者が多かった。循環器疾患や悪性新生物疾患の合併疾患の有病率に関しては、原疾患の違いによって差はみられなかった。糖尿病性腎症患者は高血圧症有病率が高く、低HDLコレステロール値を含む脂質異常患者の割合が高かった。

表4は、2年間の追跡調査を終了した1,145名を

表2　性別の患者属性

	男　性	女　性	総　数
人数	779	435	1214
年齢　(歳)	61.1±13.1	61.4±12.7	61.2±13.0
(最小―最大値)	(22.4―95.4)	(25.1―95.1)	(22.4―95.4)
透析導入時年齢　(歳)	54.1±16.0	54.3±15.3	22.4±15.8
(最小―最大値)	(15.0―90.0)	(8.0―89.0)	(22.4―95.4)
BMI　(kg/m^2)	21.2±2.9	20.2±3.1	20.8±3.0
維持透析期間　(年)	6.9±6.9	7.1±6.5	7.0±6.7
腎不全原因疾患			
慢性糸球体腎炎	29.1%	31.0%	29.8%
糖尿病腎症	27.5%	19.3%	24.5%
腎硬化症	9.9%	9.7%	9.8%
のう胞腎	3.2%	4.1%	3.5%
膠原病	0.0%	0.9%	0.3%
不明	23.9%	26.7%	24.9%
その他	6.4%	8.3%	7.1%
合併症			
心筋梗塞	5.4%	4.8%	5.2%
脳卒中	13.1%	13.1%	13.1%
閉塞性動脈硬化症	16.2%	16.1%	16.1%
高血圧症	88.2%	85.3%	87.1%
糖尿病	32.1%	23.7%	29.1%
脂質異常	48.1%	40.9%	45.6%
嗜好習慣			
現在喫煙	39.5%	7.8%	28.2%
禁煙者	35.7%	5.5%	24.9%
常用飲酒	9.1%	3.0%	6.9%
禁酒者	44.2%	12.0%	32.6%

(平均±標準偏差)または%で表示

表3　原疾患別の患者属性（年齢、BMI、透析治療期間、合併症、嗜好）

		I	II	III	多重比較または χ^2 検定比較		
		糸球体腎炎	糖尿病性腎炎	その他	I vs II	I vs III	II vs III
総数	(人)	362	298	554			
男性／女性	(人)	227／135	214／84	338／216	*		*
年齢	(歳)	57.7±12.9	62.8±11.0	62.5±13.6	**	**	
透析導入時年齢	(歳)	48.1±15.9	59.2±11.3	55.5±16.6	**	**	**
body mass index	(kg/m^2)	20.5±2.8	21.3±3.0	20.8±3.1	**		**
透析導入後期間	(年)	9.6±7.7	3.7±3.3	7.1±6.7	**	**	**
合併症	(%)						
心筋梗塞		5.5	4.4	5.4			
脳卒中		10.8	14.1	14.1			
閉塞性動脈硬化症		19.1	15.1	14.8			
悪性新生物		7.2	6.7	8.3			
高血圧症		83.4	95.3	85.2	*		*
糖尿病		5.2	100	6.5	*		*
脂質異常		43.1	56.4	41.3	*		*
嗜好習慣	(%)						
現在喫煙		28.4	29.2	27.5			
常用飲酒		9.1	7.0	5.4			

(平均±標準偏差)または%で表示
**：$p<0.05$ Bonferroniによる多重比較検定
*：$p<0.05$ χ^2検定

解析対象として、性別、原疾患別で2年間の総死亡数・心臓疾患死亡数・脳血管死亡数・悪性新生物死亡数・心不全発症数・心筋梗塞発症数・脳梗塞発症数・脳出血発症数と1,000人年あたりの粗死亡率と循環器疾患罹患率を表したものである。男女全体の粗死亡率は85(/1,000人年)であった。男性の総死亡率は88、女性は80であった。心筋梗塞罹患率は男性で14.9、女性で10.0であった。脳卒中罹患率は男性で48.8、女性で47.4であった。2年間の追跡期間では、循環器疾患罹患率には明らかな性差はみられなかった。原疾患別で見ると、糖尿病性腎症患者の死亡率が125.4と他の2群（慢性糸球体腎炎

表4 性別・原疾患別主要死因別死亡数（粗死亡率）、循環器疾患発症数（粗罹患率）一覧

性別・原疾患別死因内訳		観察人年	総死亡	心臓死	脳血管死	悪性新生物死
男 性	(738名)	1,413.5	125 (88.4)	26 (18.4)	18 (12.7)	9 (6.4)
女 性	(407名)	801.6	64 (79.8)	17 (21.2)	9 (11.2)	2 (2.5)
糸球体腎炎	(344名)	674.7	45 (66.7)	11 (16.3)	8 (11.9)	3 (4.4)
糖尿病性腎症	(281名)	526.3	66 (125.4)	16 (30.4)	8 (15.2)	4 (7.6)
その他の腎不全	(520名)	1,014.0	78 (76.9)	16 (15.8)	11 (10.8)	4 (3.9)
総 数	(1,145名)	2,215.1	189 (85.3)	43 (19.4)	27 (12.2)	11 (5.0)
性別・原疾患別死因内訳		心不全発作	心筋梗塞発症	脳卒中発症	脳梗塞発症	脳出血発症
男 性	(738名)	133 (94.1)	21 (14.9)	69 (48.8)	39 (27.6)	23 (16.3)
女 性	(407名)	81 (101.0)	8 (10.0)	38 (47.4)	29 (36.2)	10 (12.5)
糸球体腎炎	(344名)	45 (66.7)	8 (11.9)	26 (38.5)	16 (23.7)	8 (11.9)
糖尿病性腎症	(281名)	67 (127.3)	9 (17.1)	30 (57.0)	21 (39.9)	10 (19.0)
その他の腎不全	(520名)	102 (100.6)	12 (11.8)	51 (50.3)	31 (30.6)	15 (14.8)
総 数	(1,145名)	214 (96.6)	29 (13.1)	107 (48.3)	68 (30.7)	33 (14.9)

粗死亡率ならびに罹患率は(1/1,000人年)で表記

表5 死亡に影響する要因と調整ハザード比（HR）

リスク要因	(1,145名を対象) HR	(95.0% CI) 下限	上限	p	(875名を対象) HR	(95.0% CI) 下限	上限	p
年齢	1.047	1.033	1.062	<0.001	1.050	1.032	1.068	<0.001
BMI	0.955	0.905	1.008	0.096	0.969	0.910	1.033	0.333
現在喫煙	1.021	0.700	1.490	0.914	1.102	0.700	1.735	0.675
常用飲酒	1.094	0.599	1.996	0.771	0.733	0.295	1.817	0.502
血圧低値	1.175	0.816	1.691	0.387	1.339	0.863	2.076	0.192
血圧高値	1.372	0.961	1.959	0.082	1.143	0.734	1.780	0.553
脂質異常	1.059	0.777	1.445	0.716	1.019	0.698	1.488	0.923
糖尿病	1.502	1.096	2.058	0.011	1.969	1.338	2.899	0.001
アルブミン低値	2.272	1.657	3.117	<0.001	2.196	1.502	3.210	<0.001
CRP高値	1.907	1.403	2.591	<0.001	2.178	1.498	3.168	<0.001
HCV抗原陽性	1.546	1.015	2.356	0.043	1.546	0.912	2.621	0.106
心筋梗塞既往	1.205	0.717	2.024	0.482	—	—	—	—
脳卒中既往	1.276	0.886	1.840	0.190	—	—	—	—
悪性新生物既往	1.128	0.703	1.810	0.618	—	—	—	—

説明変数には、年齢、BMI、現在喫煙、常用飲酒、血圧低値（4分位最下位）、血圧高値（4分位最上位）、脂質異常、糖尿病の有無、アルブミン低値（4分位最低位）、CRP高値（4分位最上位）、HCV抗体陽性、心筋梗塞の既往、脳卒中の既往、悪性新生物の既往を投入した。（右表では、心筋梗塞既往、脳卒中既往、癌の既往を有す270名を除いた875名を対象とし、説明変数から上記3変数を除いた）

66.7、その他の腎不全患者 76.9）に比べて高く、図3で示すようにカプランマイヤーの生存分析法による解析でも有意に糖尿病性腎症患者の死亡率が高かった（$p<0.01$）。心筋梗塞罹患率も糖尿病性腎症患者で 17.1 と他の 2 群に比べて高かった。観察期間が 2 年間と短いことから、性別・疾患別に各死因別の死亡率の差を検定することは現時点で困難なものが多いが、各種死因別死亡率に性差はなさそうであること、原疾患別でみると、糖尿病性腎症患者の各種死亡率、心不全発症率、脳卒中発症率が高い傾向にあった。

図2はカプランマイヤー法による生存曲線を、性別、原疾患別に求めたものである。死亡率に性差は見られなかった（図 2-1）。原疾患別で見ると、糖尿病性腎症患者の死亡率が高かった（$p<0.01$、図 2-2）。

表5は、1,145 名を対象として Cox 比例ハザードモデルを用いて死亡に影響する要因について多変量調整ハザード比を求めたものである。死亡に有意に関連していた要因は、年齢、アルブミン低値、高 CRP 値、糖尿病合併、C 型肝炎抗体陽性があげられた。心筋梗塞合併、脳卒中合併、悪性新生物合併より、栄養不良であること、炎症反応が亢進していることが、死亡への強いリスク要因であると考えられた。心筋梗塞、脳卒中、悪性新生物のいずれかを合併していた 270 名を除いて、死亡に影響する要因について多変量調整ハザード比を求めたものを右側に載せた。重症合併症のある者を除いても、死亡に強い影響を与えていたのは、低アルブミン血症と高 CRP 値、

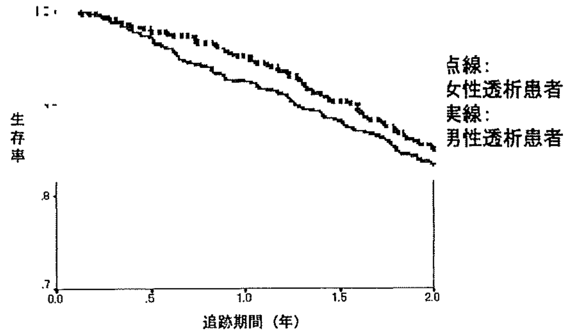

図 2-1　性別生存曲線

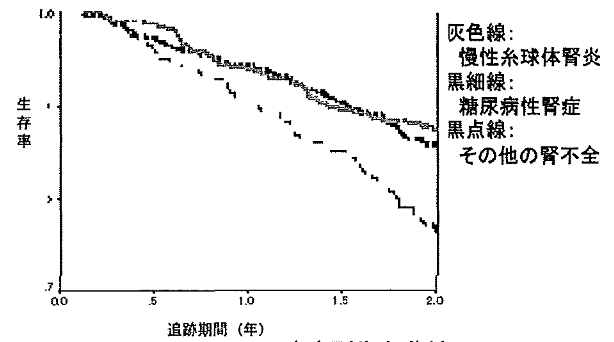

図 2-2　原疾患別生存曲線

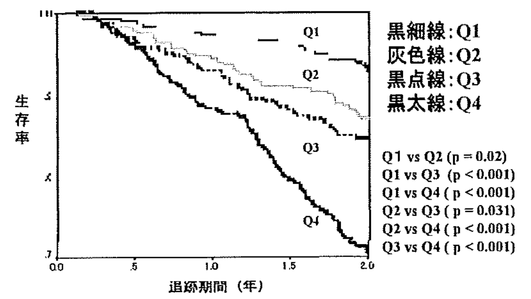

図 3-1　CRP 値 4 分位別の生存曲線

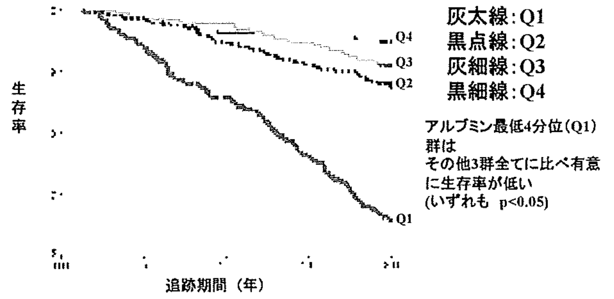

図 3-2　アルブミン値 4 分位別の生存曲線

糖尿病合併であった。

図 3 は、透析患者の死亡に強く影響していた血清アルブミン値と血清 CRP 値に着目し、4 分位別にカプランマイヤー法による生存曲線を求めたものである。血清 CRP 値と死亡との関連をみると、CRP が高くなるほど死亡率は高くなり、カテゴリが一つ上がるごとに有意に死亡率が上昇していた（図 3-1）。一方血清アルブミン値に着目すると、アルブミン低値（血清アルブミン 3.5g/dl 以下）者が他の 3 群に比べて有意に死亡率が高かった（図 3-2）。炎症反応が亢進していること、栄養不良であることが、強く死亡率を上げていることが示唆された。

IV. 考　　察

本研究結果を要約すると、研究参加透析患者 1,214 名中 1,145 名で 2 年間の追跡調査を終え、189 名の死亡を確認した。死亡率は 1,000 人年あたり 85 で、2 年間で 16.5% の患者が死亡したことになる。死亡率の性差はみられず、糖尿病性腎症患者の死亡率がほかの腎不全患者に比べ高かった。

死因の内訳を見ると、心臓血管死亡が全体の約 3 割、脳血管疾患死亡が全体の約 1 割、感染症死亡が 17%、悪性新生物疾患死亡が 6 %で、いわゆる循環器疾患死亡は全体の 4 割を占めていた。欧米の報告を見ると、心疾患死亡、特に冠動脈疾患死亡が透析患者では多いことが報告され、我々のデータは、欧米の報告に比べ、循環器疾患死亡、特に心臓疾患死亡が少なかった[2, 18]。

死亡に影響している要因を、Cox の比例ハザードモデルを用いて多変量調整ハザード比を求めると、フラミンガム研究で提示された古典的危険因子は、年齢と糖尿病をのぞくと、高血圧、高脂血症、肥満、喫煙はいずれもリスク要因とはいえなかった。一方死亡に強く影響していたのは、血清のアルブミン低値と CRP 高値であった。栄養不良と炎症反応亢進に関連するこの二つの要因は、ほかのどの要因に比べても強く死亡に影響し、循環器疾患・悪性新生物の既往よりも死亡に強く影響していたばかりではなく、上記疾患既往を有していない対象者に限定して行った解析でも、死亡に強く影響する要因であった。本研究では、透析患者の予後に影響する因子として、フラミンガム研究で示された古典的危険因子が候補に挙がらず、低栄養状態や炎症亢進が強いリスク要因であることが示されたが、これは欧米で行われた透析患者の縦断研究とよく一致している[19-27]。

欧米で行われた透析患者のコホート研究では、古

典的危険因子が透析患者の予後に強く影響しないばかりか、古典的危険因子の中でも肥満、高血圧、高コレステロール血症はむしろ予後を改善する方向に働くことが示されてきた。一般住民を対象として行われた従来の疫学調査で確立された死亡リスクを高めている要因が、透析患者・老人・貧者などではむしろ死亡率を下げる方向に働いている現象に対して、reverse epidemiologyとの名称をつけた研究者もいる[22]。我々のデータでも、有意性は認められなかったものの、BMIが高いほど、血清コレステロールが高いほど死亡率が低くなる傾向にあった。また、古典的危険因子の中で、死亡率に影響していたのは、年齢と糖尿病のみであった。死亡率に性差が認められないことも透析患者の大きな特徴である[28]。健常人では、女性であることが循環器疾患発症リスクや悪性新生物発症リスクを低め、死亡率を下げる大きな要因となっているが、本研究結果によると女性透析患者の粗死亡率、循環器疾患罹患率は男性透析患者と比べて有意に低いわけではなかった。

本研究では、C型肝炎抗体陽性者の死亡リスクが高かった。死因内訳を見ると、肝不全死亡や肝癌死亡が多いわけではなく、C型肝炎抗体陽性者は、循環器疾患死亡や感染症死亡リスクが高かった。今回の検討では、C型肝炎抗体陽性者でなぜ死亡リスクが上がるのかについては十分な検討はできなかった。C型肝炎感染によって引き起こされる栄養不良や炎症亢進が死亡リスクを上げている可能性はある。しかし、今回の検討ではC型肝炎抗体陽性は血清CRP値や血清アルブミン値とは独立して死亡リスクをあげていたことから、なぜC型肝炎感染が死亡リスクを高めるかについて今後探求する必要がある。

本研究では、循環器疾患発症についても検討した。2年間の間に、約2割の患者が心不全を発症し、約1割の患者が脳血管疾患を発症していた。心筋梗塞発罹患率は13.1であり、脳卒中罹患率は48.3と、心筋梗塞罹患率の3-4倍であった。脳梗塞に限定しても罹患率は30.7であり、心筋梗塞罹患率の2倍以上であった。

一般住民を対象としたコホート研究では、欧米では心筋梗塞罹患率が脳血管疾患罹患率より高いのに比べ、日本人では脳卒中罹患率が数倍高い[29]。一般人で観察されるこの現象は、透析患者でも同様に観察されるようである。罹患率データについては、透析患者の大規模集団で検討した例がないので、循環器疾患死亡率や循環器疾患有病率を代用して比較検討してみると、透析患者でも、米国人は心筋梗塞死亡率や有病率が脳血管疾患死亡率や有病率より高いのにくらべ[28, 30]、我々の検討では、日本人透析患者の心筋梗塞死亡率は、脳血管疾患死亡率より低く、また有病率も低い。一般人の比較では、日本人は欧米人（特に北ヨーロッパや北米）に比べ、高血圧症の有病率が高いことが、日本人の脳血管疾患発症率が高い理由として考えられる[29]。しかし、透析患者に限定すると、欧米人透析患者も我々が研究対象としている日本人透析患者も血圧がともに高く[17, 25]、血圧の違いが脳血管疾患罹患率に影響したとは考えにくい。欧米の透析患者と比較して、なぜ日本人透析患者の脳血管疾患罹患率が高く、心筋梗塞罹患率が低いのか、今後検討して明らかにする必要がある。

循環器疾患発症に影響する要因については、今回の検討では、2年間の短い期間であっても、糖尿病性腎症患者の心筋梗塞罹患率が高いことが示された。心不全発症や脳卒中罹患率についても、今後追跡期間を延ばして発症事例を増やし、罹患率の差を見出だすことが期待される。また、追跡期間が長くなり、イベント発症事例が増えることで、各循環器疾患発症に影響する要因についての検討が可能となると考えられる。

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ABSTRACT

Mortality rate and cardiovascular incidence rate in hemodialysis patients. Results of 2-year follow-up data of the KAREN Study.

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A population-based cohort study of hemodialysis patients (The KAREN Study) has been carried out in the northern part of the main island of Japan since 2003. Follow-up studies were completed on 1,145 patients 2 years after initial registration. The total observation period was 2,215 patient-years. There were 189 deaths, 214 cases of congestive heart failure, 29 cases of myocardial infarction, and 107 cases of stroke. Crude mortality was 85 (/1000 patient-years). Incident rates of myocardial infarction and stroke were 13.1 and 48.3, respectively. Cumulative mortality was 16.5%. The difference of mortality between men and women was not significant. The mortality rate in patients with diabetic nephropathy was significantly higher than those in patients with other causes of renal failure (log rank $p < 0.01$). Multivariate adjusted hazard ratios (HR) were determined by Cox regression analysis. Major risk factors for total mortality in hemodialysis patients were age (HR: (95%CI) : 1.047 (1.033-1.062)), diabetes mellitus (1.416 (1.045-1.919)), the presence of hepatitis C virus antibody (1.581 (1.043-2.395)), low levels of serum albumin (2.430 (1.785-3.308), and elevated serum CRP levels (1.944 (1.442-2.621)). These factors independently contributed to increased mortality regardless of serious comorbid conditions such as myocardial infarction, stroke, and/or malignant disease

Key Words : *Hemodialysis, mortality, risk factors, cardiovascular disease, population-based cohort study, The KAREN Study*

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

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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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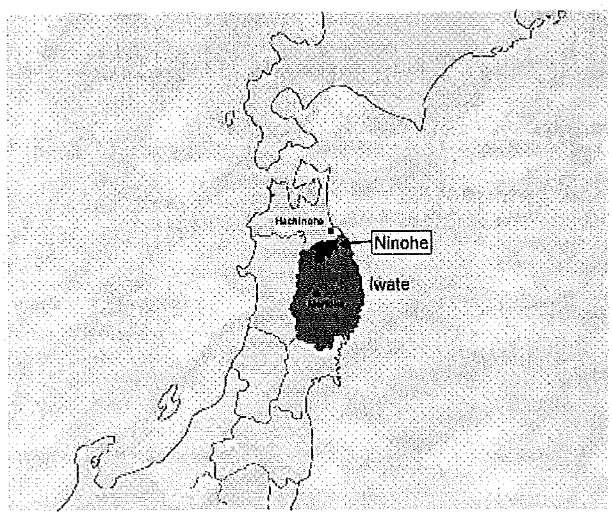

Fig 1. Study area. Ninohe district of Iwate, northern Honsyu, Japan.

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]

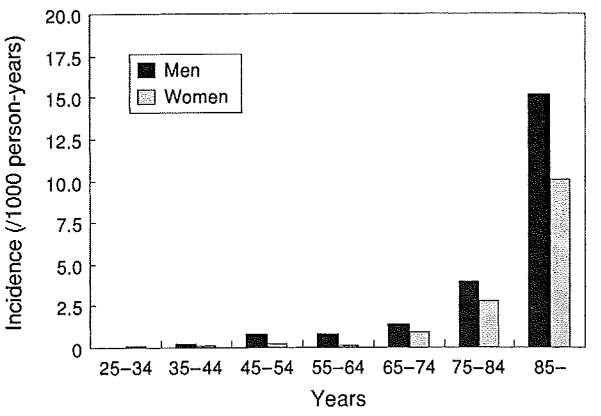

Fig 2. Incidence of heart failure according to the sex and 10-year age group.

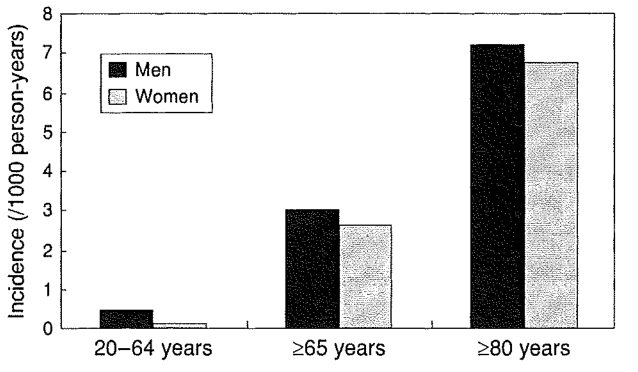

Fig 3. Incidence of heart failure according to sex and age below 65 years, ≥65 years, and ≥80 years.

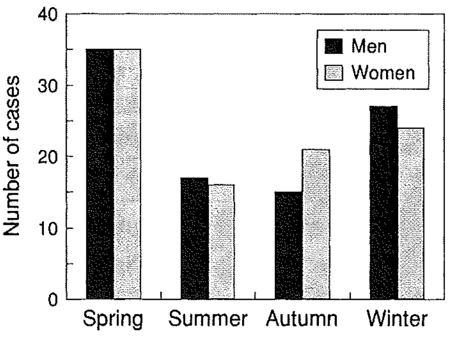

Fig 4. Seasonal variation in the accumulated number of hospitalizations for heart failure during the 3-year study period.

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 100km 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 checkups [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.